Report on **Oil of Nutmeg & Myristica Oil** 12/5/72

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REPORT

ACCESSION NO. 22

OIL OF NUTMEG
C.A.S. REG. NO. MX8007123

and

MYRISTICA OIL
C.A.S. REG. NO. MX8008455

Submitted to GRAS Review Branch (BF-335)
Bureau of Foods
Food and Drug Administration
200 C Street, SW
Washington, D. C. 20204

Att: Mr. Alan Spiher, Project Manager

Date December 5, 1972

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OIL OF NUTMEG

Summary: Toxicological Information

Historically, nutmeg was believed to have medicinal powers and was used as a sedative, carminative, antispasmodic, rubefacient, and dentifrice(66). This belief not only still survives in many parts of the world (56, 96) but has been expanded to include the use of nutmeg as an emmenagogue and abortifacient. (66) Most of the earlier reports of nutmeg poisoning are of women who had taken relatively large doses of the spice for these purposes. (27, 28).

Both the spice powder and its volatile fraction (myristic oil, nutmeg oil) appear to be psychoactive, although the powder is much superior in this regard; a synergistic action among several components has been advanced to account for this. (85). The molecular species most suspect as carrying the major psychogenic property is myristicin which is present to the extent of about 4% in the volatile extract. However, the question has been raised(78, 96)as to whether it may not in fact be due to a minor component, elemicin, recently identified and shown to be intimately associated (as an azeotrope) with myristicin.(75)

The more recent medical reports of nutmeg poisoning are of individuals whose avowed purpose was to effect mental states usually associated with narcotics and hallucinogens . In the majority of these cases, the psychological aberrations were accompanied by more or less severe physiological disturbances, often including coma. Nevertheless, full recoveries are invariably realized within days (41, 61, 67, 91, 98). "The only fatality ever attributed to the spice occurred when an eight-year-old boy ate two whole nutmegs, became comatose, and

died less than 24 hours later (96)".

Self-administered doses of the ground spice (usually mixed with water or juice) ranged from one teaspoon to a "whole can, with the onset of effects occurring 2-5 hours after ingestion. These individuals were usually seen by medical personnel some hours after the toxic effects had taken hold, so that the published reports consist mainly of descriptions of the mental experiences related by the patient to the physician. The psychological consequences of ingesting the spice varied from heightened awareness of color and sound to full hallucinogenic experiences, which have been variously reported to include distortions of space and time perceptions, feelings of unreality, floating, and having one's limbs separated from the body (21, 91, 96). There appears to be no obvious relationship between dose and effect. The anticipation of experiencing a change in affect prior to ingestion may also be an important factor in determining the degree or extent of the abnormal mental condition produced.

In an attempt to study the nutmeg poisoning phenomena in a more rational manner, a group of investigators gave 400 mg. doses of myristicin to human subjects;myristicin appears to be the psychoactive moiety of nutmeg. The only effect reported was mild cerebral stimulation. One subject (a member of the investigating team) ingested 15g. of nutmeg powder and reported to his colleagues any physical or mental changes he experienced over a period of several days. During that time, he suffered vasomotor instability, tachycardia, hypothermia, absence of saliva, constricted pupils, some emotional lability, feelings of isolation and inability to carry on intellectual processes (85).

In sharp contrast to the reports in the medical literature attesting to the psychoactive effects of nutmeg, is a study performed with univer-

sity students, some of whom received nutmeg (6g) and others a placebo, to establish whether or not the psychological aberrations are a result of drug action or of self-suggestion. The results appear to confirm the latter and the author concludes that "Nutmeg has no psychological effect in the areas of behaviour sampled when given in this quantity. It seems highly unlikely that it has any effect when given in larger amounts, and it therefore seems most probable that reports of its effectiveness are based entirely upon subjective experiences induced by the suggestiveness of the conditions under which it is taken."(5)

Nutmeg and synthetic myristicin both demonstrate a mild degree of monoamine oxidase (MAO) inhibiting activity in vitro and in vivo (89). Oral doses of 0.2 and 1.0 gm/kg nutmeg powder (as an acacia suspension) were given to mice and rats; similar doses of natural and synthetic myristicin were also administered. The onset of the inhibiting action was first noted 17-24 hours after feeding as a lowering of the convulsive threshold in mice following intravenous injection of tryptamine. In rats, after the tryptamine injection, the MAO inhibition took the form of an increase in concentration of 5-hydroxytryptamine in the brain (87). Other volatile components of nutmeg such as borneol, geraniol, and safrole did not show MAO-inhibiting activity.

The cat seems to be particularly sensitive to nutmeg and especially to myristicin. A 5-10g. oral dose of nutmeg is sufficient to cause the cat to succumb while as little as 50 mg/kg of myristicin injected intraperitoneally will result in death. The major pathological finding in these animals is fatty degeneration and necrosis of the liver (66, 85, 56). In comparison, other animals are relatively insensitive to the spice. The LD_{50} in rats for myristicin administered i.p. is greater than 1000 mg/kg(85), while for oral administration of nutmeg oil, the LD_{50} is 2620 mg/kg(42).

OIL OF NUTMEG

Chemical Information

I. Nomenclature

A. Common names (31 a, 55 a)

- Oil of Nutmeg, Expressed

  Nutmeg butter

  Oil of mace

- Oil of Nutmeg, Volatile

  Oil of myristica

  Nutmeg oil

- Nutmeg (dried ripe seed)
- Mace (dried arillode which envelopes the shell containing the seed)

B. Chemical names

(none)

C. Trade names (31 a)

- East Indian Nutmeg and Mace

  Bunda Nutmegs and Mace

  Siauw " and Mace

  Penang " " "

  Papua " " "

  Java Estate Nutmegs and Mace

- West Indian Nutmeg and Mace

D. Chemical Abstracts Services Unique Registry Number

Oil of Nutmeg - MX8007123

Myristica Oil - MX8008455

II. Empirical Formula

Oil of Nutmeg refers to both the volatile fraction obtained by steam distillation and to the so-called fixed oil obtained by pressing the crushed nutmegs between heated plates. Each of these oils is a mixture of substances, with the major components of each type being: (31 a)

Volatile Nutmeg Oil

d-Pinene		$C_{10}H_{16}$
d-Camphene		$C_{10}H_{16}$
Dipentene		$C_{10}H_{16}$
d-Linalool		$C_{10}H_{18}O$
d-Borneol		$C_{10}H_{17}OH$
dl-Terpineol	about 6%	$C_{10}H_{18}O$
Geraniol		$C_{10}H_{18}O$
Myristicin	about 4%	$C_{11}H_{12}O_3$
Myristic acid, free	0.3%	$CH_3(CH_2)_{12}CO_2H$

Recent work has also identified methoxyeugenol, trans-isoelemicin(76), and 4-terpineol (9) as components of the volatile oil.

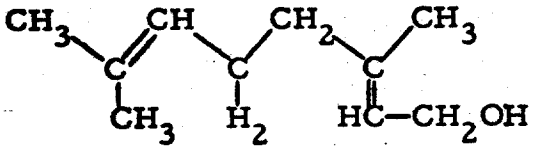
Expressed Nutmeg Oil

trimyristin (glyceryl myristate)	(approx) 73%
volatile fraction	12.5%
fat (glyceryl oleate and linoleate)	3.5%
unsaponifiable residue	8.5%

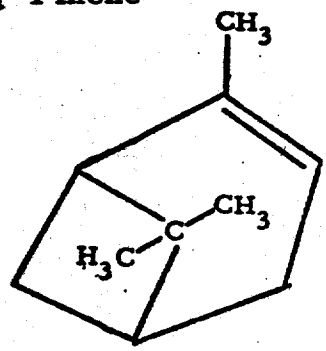
Recent work (60) has identified the component glycerides of nutmeg butter. The fully saturated fraction was present to the extent of 71.3%; the mono-unsaturated/disaturated fraction was 20.5%, and the di-unsaturated mono-saturated fraction was 8.2%. After conversion to fatty acids all of the saturated acid in nutmeg seed fat was myristic acid, whereas palmitic acid was the only saturated acid found in the mace fat(57).

III. Structural formula

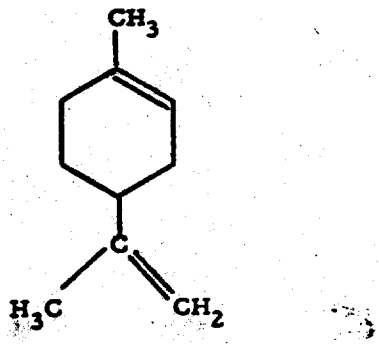
Geraniol



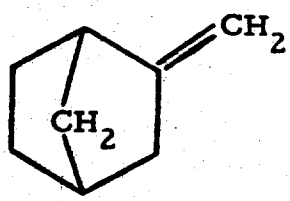
α-Pinene



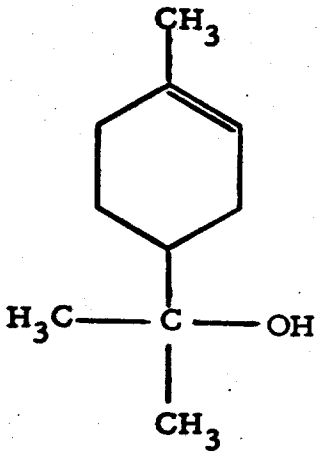
Dipentene



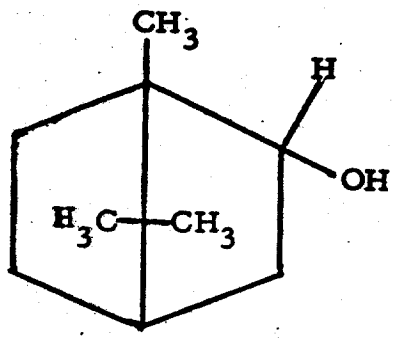
Camphene



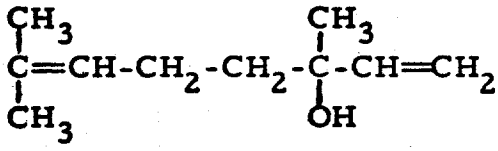
α-Terpineol



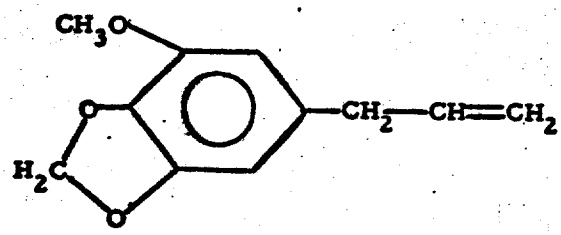
Borneol



d-Linaloöl



Myristicin



IV. Molecular weights

d-Pinene	136.13
d-Camphene	136.13
Dipentene	136.13
d-Linalool	154.14
d-Borneol	154.14
dl-Terpineol	154.14
Geraniol	154.14
Myristicin	192.10
Myristic acid, free	228.22

V. Specifications

A. Chemical

(none)

B. Food Grade (20 a)

Residue on evaporation

East Indian: Not more than 60 mg.;

West Indian: Not more than 50 mg.

Limits of Impurities

Arsenic (as As). Not more than 3 ppm (0.0003 %).

Heavy metals (as Pb). Not more than 40 ppm (0.004 %).

Lead. Not more than 10 ppm (0.001 %).

C. Official Compendia

Food Chemicals Codex, 1st Ed. 1966.

VI. Description

A. General characteristics

The volatile oil obtained by steam distillation from the dried kernels of the ripe seed of Myristica fragrans Houttuyn (Fam. Myristicaceae). Two types of oil, the East Indian and the West Indian, are commercially available. It is a colorless or pale yellow liquid, having the characteristic odor and taste of nutmeg. (20 a)

B. Physical Properties

Angular rotation

East Indian: Between +8° and +30°

West Indian: Between +25° and +45°

Refractive index

East Indian: Between 1.4740 and 1.4880

West Indian: Between 1.4690 and 1.4760 at 20°

Specific gravity

East Indian: Between 0.880 and 0.910

West Indian: Between 0.854 and 0.880

C. Stability in containers, animal feeds, etc.

Store in full, tight containers in a cool place protected from light.

VII. Analytical Methods

- GLC and mass spectrometry to identify the major components of nutmeg oil. (70)
- Distillation techniques using liquid traps of varying density to resolve the volatile components (12).

- Gas chromatography of oil of nutmeg to distinguish among closely related varieties of the oil. (6)

VIII. Occurrence and levels found in:

A. Plants

Nutmeg (myristica) and mace are both derived from the fruit of Myristica fragrans Houtt. (fam. Myristicaceae), nutmeg being the dried ripe seed, and mace the dried arillode which envelops the shell containing the seed or nutmeg. They owe their characteristic aroma chiefly to the presence of an essential oil which can be isolated by steam distillation. Oil of nutmeg and oil of mace are very similar in odor and flavor, and since the nutmeg suitable for distillation is usually lower priced than mace, the former is generally employed for commercial production of the volatile oil. (31a) Different varieties of nutmeg contain from 5-15% of the volatile oil. (85) The component myristicin occurs with the related substance apiole in parsley (92).

B. Animals

(none)

C. Synthetics

(none)

D. Natural inorganic sources

(none)

OIL OF NUTMEG

Biological Data

I. Acute Toxicity

Animal	Route	Material	LD_{50}(mg/kg)	Ref.
Rat	oral(intubation)	nutmeg oil	2620	42
Rat	i. p.	myristicin	>1000	85
Rat	oral	E. Indian nutmeg	500±140	85
Rat	oral	W. Indian nutmeg	700±250	85
Rat	oral	E. Indian nutmeg after removal of volatiles	1720±590	85
Rat	oral	W. Indian nutmeg after removal of volatiles	1730±400	85
Rat	oral	nutmeg oil	2600±220	20 b
Mouse	oral	nutmeg oil	5620±520	20 b
Hamster	oral	nutmeg oil	6000±230	20 b

II. Short-term Studies

(none)

III. Long-term Studies

(none)

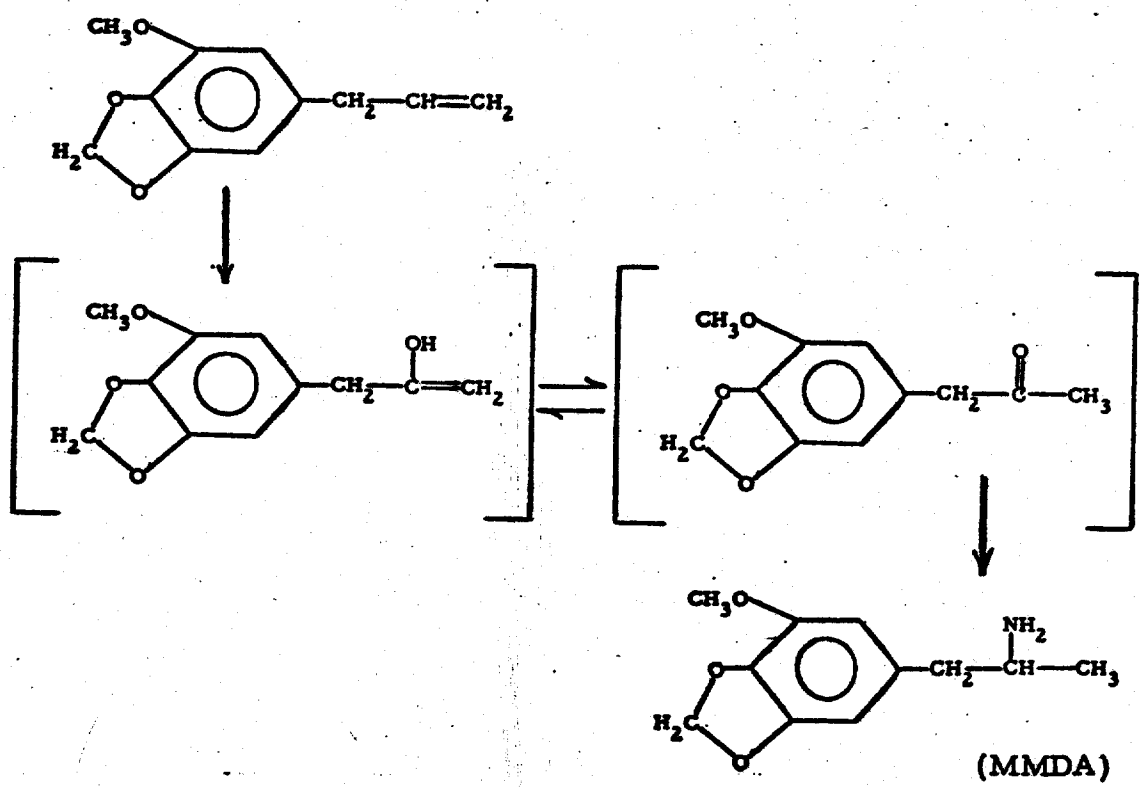
IV. Special Studies

(none)

Biochemical Aspects

Biochemical and related data were not found in the abstracts received nor in the literature scanned, however the in vivo conversion of myristicin to the known psychotomimetic agent 3-methoxy-4, 5-methylenedioxy amphetamine (MMDA) has been suggested to account for the reported psychoactivity of myristicin. (96) Myristicin is the major component of volatile nutmeg oil suspected of having psychoactive properties.

myristicin



(MMDA)

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Case No. 3.—A cabinet-maker, aged 38, was unable to move without great difficulty on account of severe lumbago. Relief began within sixty seconds of injection. In five minutes there was complete relief of pain. Side-effects were troublesome, and consisted of blurred vision, faintness, and sweating. Treatment was continued with oral orphenadrine, 100 mg. twice daily, plus an analgesic ('Zactirin'), two tablets three times a day. The patient returned to work in two days.

SUMMARY

A trial of orphenadrine citrate ('norflex') on 64 patients with muscular pain showed a favourable response in 31 patients, and a doubtful result in 13.

Suggestions are made as to why a centrally acting muscle relaxant such as orphenadrine might be effective, when peripherally acting relaxants are disappointing.

A small comparative trial between orphenadrine and analgesics in the same patients suggested that orphenadrine produced better results in nine out of 17 patients, and equal results in five.

Orphenadrine given by injection to seven patients with severe pain, produced dramatic improvement in six.

I wish to thank Riker Laboratories for generous supplies of 'norflex' tablets and 'norflex' injection.

NUTMEG POISONING

By J. H. REES, M.B., B.S.
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The culinary nutmeg weighs about 5 grammes and is obtained by drying the seed kernel of *Myristica fragrans*—an evergreen tree grown in both Indonesia and the West Indies. In addition to its culinary uses, it has been used medicinally as a sedative, carminative, antispasmodic, rubefacient and dentifrice.

Early this century its alleged emmenagogue and abortifacient properties resulted in cases of poisoning being reported. More recently, its ability to induce a state of euphoria has attracted it to alcoholics and drug addicts deprived of their normal supplies.

Poisoning usually follows within six hours of the ingestion of one or more nutmegs. Cushny (1908) described the main symptoms as drowsiness with disorientation passing through delirium to stupor, and considered that they pointed to a mixed action on higher parts of the central nervous system. Dryness of the mouth, causing thirst, anorexia, vomiting and abdominal discomfort, may result from the direct local action of nutmeg.

A nibbling habit, more pronounced at times of stress, seems to have resulted in poisoning in the case now reported.

CASE HISTORY

A healthy 42-year-old woman, the mother of six children, whose ages ranged from 7 to 20 years, had no liking for sweets or cigarettes. She preferred to nibble in her kitchen and thus found that nutmeg satisfied her wish for something spicy.

Two days of her week were spent as a collector and nutmegs were bought to sustain her on her rounds. Two years previously she recalled being unable to arise from bed, and, the doctor attending noted her labile mood and concern about a son in the Navy, but dismissed her nutmeg theory as he considered her to be in a 'pre-psychotic' state. A full recovery followed a weekend in bed.

The habit, which was likened to the longings of pregnancy, had been indulged in periodically since. She sought advice because twice in the previous month the following toxic symptoms had resulted from the ingestion of three to six nutmegs.

Concentration became difficult and her thoughts disjointed. The figures in her book seemed meaningless and once, although aware that her child was addressing her, she was unable to understand what was being said. She felt self-conscious and hypochondriacal ('a most unusual state') and was uncertain whether recently performed tasks had been done. Things did not seem as they should be and she felt 'outside herself'. Her emotions were difficult to control; irritability, laughing or crying would occur and the startled expression on a customer's face suggested that something outrageous had been said.

There was a sense of weariness and of difficulty in walking and people commented on her pale, drawn features. Flushing alternated with shivering and she noted that her pupils were usually pinpoint in size. Dryness of the mouth was denied, emphasis being made of the refreshing sense in the mouth and of the whiteness of her teeth. Her digestion, bowels and micturition were unaffected. The menses, however, had occurred twice as frequently (fortnightly) during the previous two months.

The effects would appear about an hour after beginning to nibble and become progressively more troublesome as the day proceeded. Bed was associated with a pleasant, almost hilarious sense of drifting off to sleep. The main symptoms disappeared by the following morning although a sense of utter exhaustion would be apparent for a day or two and a week would elapse before recovery was complete.

The two recent toxic episodes coincided with a period of anxiety concerning the behaviour of an adolescent son.

By the time she sought advice, the effects had worn off and examination showed no abnormality. The habit was stopped without difficulty and her periods returned to normal. Twelve months later she remains well and sums up her toxic state as having been 'mental rather than physical—as if I were drunk'.

The absence of marked physical reaction, especially of dryness of the mouth, in this woman is unusual and might be explained by her acquired taste for nutmegs and the relatively slow ingestion of toxic dosage.

OTHER CASE REPORTS

The diversity of effects produced is brought out by comparison with two other reported cases, in both of which laboratory investigations were performed.

Green (1959) noted that a woman who had taken 18.3 g. of powdered nutmeg to induce menses, awoke seven hours later complaining of a burning sensation in her abdomen and a sense of impending death. Disorientation with wild excitement and thrashing of limbs followed until semi-stupor supervened a few hours later. Excitement and fear returned after another twelve hours to give way to a sense of numbness and sleepiness lasting two more days. An initial albuminuria, with a fall in the serum sodium and potassium levels but normal chlorides, was noted. The blood count and liver biopsy were normal.

McCord and Jervey (1962) reported that a man, taking two nutmegs to disperse a pustule on the neck, complained of dryness of the mouth, warmth and perspiration. Dyspnœa, pains in the chest and a sense of impending disaster followed. He was found to be anxious and hyperventilating although apyrexial. Tachycardia and hypotension were noted. The electrocardiogram showed non-specific changes and urinalysis was negative. The blood count, blood sugar and blood cholesterol were normal, as also were repeated serum glutamic oxalacetic transaminase. He was able to return to work twenty-four hours later.

DISCUSSION

Pyrexia, allergic swelling and pruritus of the face, insomnia, hyperactivity, choreiform movements and transient hypertension have also been reported, whilst Payne (1963), noting that dilatation of the pupils might occur, considers constriction an early feature. Symptoms usually clear within twenty-four hours although dryness of the mouth, fatigue, sleepiness and a sense of numbness and unreality may persist for a few days. Coma and death have been reported in an eight-year-old boy who ate two nutmegs (Cushny, 1908). There is no evidence to suggest that addiction occurs, even when side-effects are minimal.

Pharmacology.—The active ingredients are found in the volatile oil that forms some 5 to 15 per cent. by weight of nutmeg; 88 per cent. of this oil consists of the inert pinene, camphene, and dipentene.

Toxicity is associated with the high boiling constituents and, of these, myristicin, forming some 4 per cent. of the oil, is thought to be the poisonous principle. Cushny (1908) noted that it produced depression and paralysis of the central nervous system in lower animals with little, or no, effects on peripheral nerves, muscles or heart. Dale (1909) reported that both nutmeg and myristicin caused death from fatty degeneration and necrosis of liver in cats, but thought that, unlike what happens in man, the central nervous system of lower animals remains unaffected until dosage is massive enough to cause liver failure. Power and Salway (1908) stated that the dosage of myristicin necessary to produce these effects, was proportionally greater than that obtained with nutmeg, and concluded that the other constituents of nutmeg might aid the absorption of myristicin.

Fifty years later, Weiss (1960), reporting on the hallucinogenic properties of powdered nutmeg, noted that prisoners compared its narcotic-like effect to marihuana. He considered that eugenol, another of the high boiling constituents, might be responsible for the euphoria produced. Truitt and his colleagues (1961) noted that there was a special structural relationship between the formulæ of myristicin and adrenochrome, a serotonin antagonist. They were unable to reproduce in man, with myristicin alone, the full picture of nutmeg intoxication and concluded that most of the psycho-pharmacological effects were due to the other volatile constituents present. Three of these—eugenol, isoeugenol and safrole—form about 0.8 per cent. of the oil and, like myristicin, are catechol derivatives, whilst terpineol, genaniol, linaloöl and borneol account for about 6 per cent. (Power and Salway, 1907). They are found in varying quantities in many of the perfumes and spices long cherished by man. It is of interest to note that save for the absent amine radicle, the side chains of the catechol derivatives resemble superficially those found in many of the mood elevators in use today.

SUMMARY

The subjective sensations are described of a woman who nibbled nutmeg. The features suggest a mild toxic psychosis.

Attention is drawn to various other effects ascribed to this common spice and, in view of the long interval since a case of nutmeg poisoning was last reported in this country, an account is given of the poisonous factors.

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A CONTROLLED-RELEASE IRON TABLET

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In a survey of anæmia which was undertaken in this Health Centre in 1956, a large amount of sub-clinical anæmia was discovered. Subsequent periodical checks have shown that for a variety of reasons the treatment was not altogether satisfactory as patients tended to give up taking iron tablets before the completion of treatment. It was found that:

(1) All tablets seemed to produce one or more side-effects, such as diarrhœa, vomiting, indigestion.
(2) Patients, particularly pregnant women who have various other preparations to take also, found it a chore and a bore to have to take pills so often and over such a long period.

SCOPE OF INVESTIGATION

It therefore became obvious that for the successful treatment of iron-deficiency anæmia, a preparation having the advantages of minimal dosage and no side-effects was needed. When a new preparation conforming to both these requirements was produced, a clinical trial of the tablet in question was instituted in this practice.

The tablet used in a double-blind trial was 'ferro-gradumet'. This is a 'controlled-release' tablet, which contains 525 mg. of exsiccated ferrous sulphate (equivalent to 105 mg. of iron), the main part of which is released in the small intestine. It is claimed by the makers to produce minimal side-effects, and to have the advantage of requiring only one tablet to be taken each day.

Twenty-two patients, selected at random, took part in the trial, eleven being given 'ferro-gradumet', and the rest the control tablet (containing lactose), the dosage being one tablet per day given over a period of two

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NUTMEG (MYRISTICIN) POISONING

A CASE REPORT

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The following case seems worthy of presentation because it illustrates a relatively rare form of intoxication, the manifestations of which may be dismissed by the unsuspecting examiner as an anxiety reaction.

Case Report

A 41 year old building contractor was admitted to the Medical College Hospital on January 22, 1962 because his physician feared that he might have an impending myocardial infarction. Because of a small pustule on his neck, he had for several days taken Fowler's Solution with potassium iodide (10 drops three times daily) prescribed by a pharmacist friend. Finally, a friend suggested that the ingestion of nutmeg might help his skin infection. On this advice, he bought several nutmegs from a grocery store and proceeded to eat two of these whole on the morning of the day of admission. That afternoon he noted some malaise and went to bed. His mouth seemed dry and he was mildly nauseated. He experienced feelings of warmth with increased perspiration. After sleeping most of the afternoon, he awoke feeling hungry and ate a large dinner. Following this, he felt as though "things were closing in," became weak and experienced a sense of impending disaster. He began to breathe more rapidly than normal, and had vague, fleeting pains in his chest and left arm. These sensations recurred in episodic form at gradually shorter intervals. At one point, when the attacks were about two minutes apart, he felt certain that he would die. It was necessary that an ambulance be summoned to bring him to the hospital emergency room. Here he was noted to be anxious, hyperventilating and hypotensive with a systolic blood pressure of 80 to 90 mm. Hg.

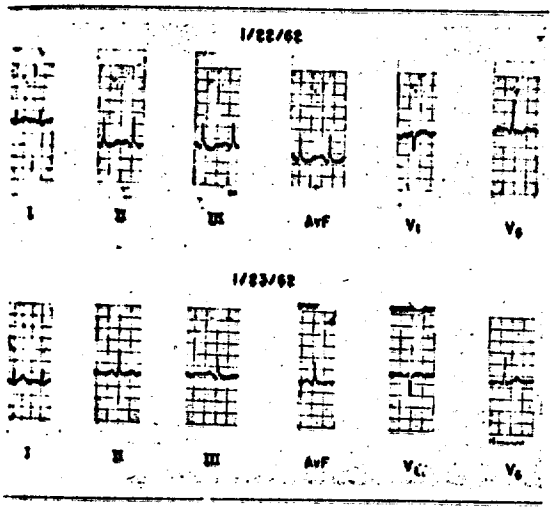
No immediate treatment was prescribed. By the time of arrival at his hospital room, he was much improved. Examination revealed a well developed and anxious man. Temperature 98°F. Pulse [illegible]. Respirations 26. Blood pressure 120/60. Examination of the upper respiratory tract was normal. A small pustule was present on the posterior aspect of the neck. The heart and lungs were normal. The abdomen was relaxed and no organs or masses were palpable. There was no cyanosis and the temperature of the extremities was normal. The remainder of a complete physical examination was within normal limits.

His past health had been good except for an episode of hemoptysis four years previously which prompted hospitalization. Bronchoscopy and bronchograms done at that time were normal and he was

fered no recurrence of this disorder. He had been a heavy smoker and had always been "somewhat nervous," although he had never received treatment for any psychiatric disorder. There was a family history of diabetes.

Laboratory studies on admission showed hemoglobin 13.3 Gm., RBC's 5.5 mil., WBC's 10,800 (Polys 70%, Lymphs 26%, Monos 3%, Eos. 1%). Urinalysis negative. Fasting blood sugar 81 mg./100 ml. Blood cholesterol 205 mg./100 ml. Daily serum glutamic oxalacetic transaminase determinations on the three days of hospitalization were 17, 18 and 13 units respectively. Urine collected for 24 hours was negative for arsenic.

An electrocardiogram taken in the emergency room showed flattening and early inversion of T-waves with slight prolongation of the Q-T interval considered to be non-specific and compatible with changes seen with hyperventilation. An electrocardiogram the following morning was completely normal (Figure). A chest x-ray film was negative.



The patient remained afebrile throughout his hospital stay and his pulse slowed to a normal of 80 to 90 during the first 24 hours. By the morning after admission he felt well except for dryness of his mouth and he was anxious to return to work. His blood pressure remained stable between 110 to 130 mm. Hg. systolic and 70 to 80 mm. Hg. diastolic. No treatment was necessary except for bedtime sedation.

The admission impression was that of an acute anxiety reaction with electrocardiographic abnormalities secondary to hyperventilation. The possibility of an early myocardial infarction was considered less likely. The quantity of arsenic and potassium iodide ingested seemed too little to account for his symptoms, and his illness would have been dismissed as an anxiety reaction had not one of the authors recently read a description of nutmeg poisoning in children. This fortuitous recollection prompted a search of the literature which revealed descriptions of similar states following nutmeg ingestion and led us to conclude that our patient in all probability fell into this category.

Comment

A number of cases of nutmeg poisoning following the ingestion of one to three whole nutmegs or an equivalent amount of the ground condiment appear in the literature. The occasional misuse of this common kitchen spice has been the result of "old wives tales" describing its ability to induce abortion and to cure boils and various other conditions.

The essential oil of nutmeg and its chief toxic component is the phenolic compound myristicin (1 - allyl, 3 - methoxy, 4,5 - methylene dioxide benzene).[9-11, 13] This is a yellowish liquid with a specific gravity of 1.1425 and a boiling point of 149.5°C. Although nutmeg has been used medicinally in the past it appears to have little therapeutic value.

Dale[9] studied the toxic effects of whole nutmeg and myristicin in cats. Oral administration first resulted in vomiting, salivation and decreased appetite. These symptoms were followed in 2 to 3 days by the development of jaundice and coma, the loss of corneal reflexes, dilation of the pupils, slowed heart rate and respirations, decreased body temperature and finally death. Subcutaneous administration of myristicin produced similar findings with delayed death. Pathologic examination of these animals showed advanced fatty degeneration of the liver in all cases.

von Oettingen[13] reviewed the reports of toxicity in other animals including frogs, dogs, rabbits and guinea pigs, and noted a general depression of the central nervous system in all. Isolated guinea pig uterus showed some increased tone with the direct application of myristicin in Tyrode's solution. Isolated rabbit intestines showed decreased tone and a reduced number of contractions with similar treatment.

Myristicin toxicity in man is illustrated by the following cases reported in the literature: Beck[9] described two young women who ingested two ground nutmegs added to wine, hoping to induce abortion. Following ingestion

of the drink they experienced dyspnea, some loss of memory and drowsiness. Both were found unconscious with weak, rapid pulses. Later, some "motor disturbances" developed with further increase in the pulse rate. From this state both patients recovered fully in three to five days without residual effects.

Mendelsohn[3] reported the case of a young man who ate two to three pieces of ground nutmeg for eczema associated with varicose veins. Following ingestion he experienced muscle weakness, dyspnea, dryness of his mouth and loss of memory. Finally he fell into a deep sleep but he recovered the following day with only slight fatigue.

A second case reported by the same author was a woman with menopausal bleeding who ate three nutmegs. She presented with severe agitation, fine tremor, restlessness, delirium, cold extremities and a weak rapid pulse. She recovered in two days.

Hammond[4] reported a similar case of a woman who, following ingestion of a grated nutmeg, developed nausea and vomiting, dizziness, coldness, restlessness and substernal pressure. Her pulse was rapid and weak and her respirations shallow and irregular. She too recovered the following day.

In other reports[1, 2, 5, 7, 10, 13, 14] patients have consumed from one to three nutmegs and have experienced restlessness, dizziness, fear of death, coldness of the extremities, occasional nausea and vomiting, abdominal pain and precordial pain or oppression. These patients were often found to be extremely agitated, delirious, and dyspneic and have had weak rapid pulses, and decreased body temperature. On several occasions patients were found unconscious. Occasionally there was flushing of the face while at other times pallor with cyanosis of the lips and nails predominated. Rare cases have displayed facial and periorbital edema associated with flushing. It is interesting that of all the instances reviewed in which nutmeg was taken as an abortifacient, this effort was successful in only one patient. Even in this instance the role of nutmeg was open to question since the abortion followed the ingestion by a period of a month. In this review, we found no documental report of a fatality due to nutmeg ingestion, although such an occurrence in a child was mentioned by Dale.[4]

Thus it is seen that nutmeg, if taken in large enough quantities, is toxic for man and animals. In man, because of a more sensitive nervous system, neurotoxic effects are more pronounced and occur at low concentrations while in animals (including cats), the nervous system is less susceptible, and doses of myristicin sufficient to produce minimal neurotoxicity usually lead to delayed death due to liver failure.

In the cases reported, myristicin toxicity appears to have resulted primarily from a central nervous system depressive effect with periods of stimulation and associated respiratory and cardiovascular difficulties. Occasional case reports have suggested a possible hypersensitivity reaction as illustrated by the presence of facial and periorbital edema with flushing.

Although we cannot be dogmatic, we feel that the symptoms displayed by this case were sufficiently similar to those reported by others to warrant the conclusion that our patient suffered from mild nutmeg (myristicin) poisoning. It is hoped that this brief review may serve to increase the general awareness of this rare but interesting disorder.

Summary

A case of poisoning due to the ingestion of nutmeg is reported. The toxic component of nutmeg is the chemical, myristicin. The toxic effects of this compound in man and animals have been reviewed. Nutmeg, if ingested in sufficient quantities, can produce distress and serious disturbances in man.

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Requests for reprints to Dr. Jervey, Dept. of Medicine, Medical College of South Carolina, 55 Lucas St., Charleston, S. C.

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MANAGEMENT OF ALCOHOLIC WITHDRAWAL
OBSERVATION USING CHLORDIAZEPOXIDE AS CHIEF TRANQUILIZING AGENT

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The management of symptoms of acute alcoholic withdrawal may be difficult and is usually complicated by problems of nutrition, gastric irritability, imbalance of electrolytes, central nervous dysfunction and psychiatric abnormalities. Because alcoholism is a multi-faceted medical problem, there is no single "panacea" drug available for the management of the withdrawal symptoms. Among the medications and therapeutic regimen that have been reported beneficial in the management of withdrawal from alcohol, chlordiazepoxide (Librium) has been recently singled out as an outstanding adjunct to therapy.[1-6]

This study concerns our experience with chlordiazepoxide as the chief tranquilizing agent in the management of 35 consecutive alcoholic patients hospitalized during the acute withdrawal period. The duration of pathologic drinking and the length of individual alcoholic bouts for this group is tabulated in Tables 1 and 2.

Method: Upon admission to the hospital, each patient was given intravenously 1,000 ml. of Baxter's #2 electrolyte solution to which was added a multivitamin preparation. In addition, patients were given initially chlordiazepoxide 100 mg. intramuscularly, reinforced when necessary with promazine or chlorpromazine 50-100 mg. intramuscularly. The latter was given in instances of extreme agitation, belligerency and situations not quickly brought under good control with the chlordiazepoxide initially given. For the first 24 hours chlordiazepoxide was continued as intramuscular medication, 50-100 mg. every 3-4 hours; later this same dosage was continued as oral medication, being maintained as long as psychomotor agitation and coarse tremor were observed. As the patient improved, the dosage and frequency of administration was gradually diminished. Parenteral vitamins

TABLE 1
Duration of Pathological Drinking

	1 year	1-3 years	3-5 years	5-10 years	10-20 years
# Patients	9	6	11	5	5

TABLE 2
Duration of Present Bout

Weeks.	Under 1	1	2	Over 2
# Patients	6	15	5	9

The use of nutmeg as a psychotropic agent[1]

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Introduction

In his search for varied experience and escape from everyday boredom, man has found many substances of plant origin that poison the human organism but that, at the same time, cause pleasurable physical or mental changes. The word "narcotic" technically denotes a stupor-inducing drug, but it has been loosely applied to many of these deliberately-consumed substances. Narcotics are used regularly in nearly all parts of the world, and three observations about these practices are relevant to this paper. First, man seems willing to experiment with almost anything in his environment to find new intoxicants: such bizarre materials as certain glues, morning-glory (*Ipomœa*) seeds, cinnamon, and spider webs have all been put to narcotic use.

Second, persons who take narcotics often must tolerate extreme discomfort along with the pleasant effects produced by drugs.

Third, psychological factors profoundly influence individual reactions to narcotic drugs. A person seeking euphoria may find it in a chemical that does little on its own but cause dizziness.

The use of nutmeg as a narcotic illustrates all three points: nutmeg is an obscure drug, causes many alarming symptoms, and brings about pleasant mental changes only in the proper psychological context. Yet nutmeg must be considered a narcotic not only because it can induce stupor but also because many persons now consume it deliberately to escape reality.

Botanical, historical, and commercial notes on Myristica fragrans

Nutmeg and its sister-spice mace are both products of the nutmeg tree, *Myristica fragrans* Houtt. (Myristicaceae). The genus comprises about 100 species found throughout the tropics, especially in the Malayan region; but of these, *M. fragrans* alone contains enough of an aromatic essential oil to make it valuable for cultivation. Nutmeg is the dried seed of the plant; mace is the dried aril surrounding the shell enclosing the seed (figs. 1 and 2).

The nutmeg tree requires a hot, humid climate, and is widely cultivated in the tropics, particularly on the Spice Islands (the Moluccas), around the Strait of Malacca, and in the Caribbean (notably on Grenada).

Products of Myristica: *their uses and composition*

The finest mace and the finest nutmegs come from Penang, and, in general, the East Indian spices are preferred to the West Indian.

Nutmeg husks

The pericarp of the nutmeg fruit can be preserved in sugar while unripe, salted and dried as a condiment, or made into jellies. All of these preparations have the flavour of nutmeg.

Nutmeg

Ground nutmeg, a granular orange-brown powder with characteristic aroma, is a widely-known kitchen spice. It has a warm aromatic, slightly bitter taste and is often added to custards, puddings, pies, certain vegetables, and milk drinks like egg-nog. In the past, nutmeg was much used in medicine.

Whole nutmeg, depending on the variety, contains from 5 to 15 per cent of a volatile oil that accounts entirely for the aroma and flavour of the spice.

Mace

Mace, though not quite so well-known in the kitchen as nutmeg, is none the less a popular spice. It is a brownish-yellow or brownish-orange granular powder with a strong aroma closely resembling but not identical to that of nutmeg. The flavour of mace is softer and somewhat less pungent than the flavour of nutmeg. Mace is

[1] This article is revised and adapted from "Nutmeg as a Narcotic", published in Economic Botany *19* (3): 194-217, 1965. Originally presented as a thesis for honors to the Department of Biology, Harvard University, 1964. Acknowledgment is gratefully given to Dr. Richard Evans Schultes of the Harvard Botanical Museum for his help in organizing this paper.

Note. Figures in parentheses refer to references, p. 22.

FIGURE 1

Myristica fragrans. *Top: male flowering branch Middle: female flowering branch with two ripe fruits; the pericarp has split, revealing the mace-enclosed seed. Bottom: details of fruit and seed structure. (Drawing after Rumphia.)*

used in the manufacture of pickles and tomato ketchup, in meat and fish sauces, in chocolate dishes, cherry pie and pound cake. Like nutmeg, mace has been used in medicine.

Whole mace contains from 4 to 14 per cent of a volatile oil very similar to that found in nutmegs (2, Vol. V), along with moisture, fat, starch, etc.

Fixed oil of nutmeg

The fixed oil of nutmeg is known by many names: nutmeg butter, balsam of nutmegs, "oil of mace", "butter of mace", "Banda soap", and *Oleum Myristicae Expressum*. It is obtained by exposing the nuts to hydraulic pressure and heat.

Essential oils of nutmeg and mace

The essential or volatile oils of nutmeg and mace are obtained by steam distillation. In commerce, both products go under the name "oil of nutmeg" (officially, Myristica oil or *Oleum Myristicae*), and, in fact, the commercial oil probably is distilled only from nutmegs since they are cheaper than mace.

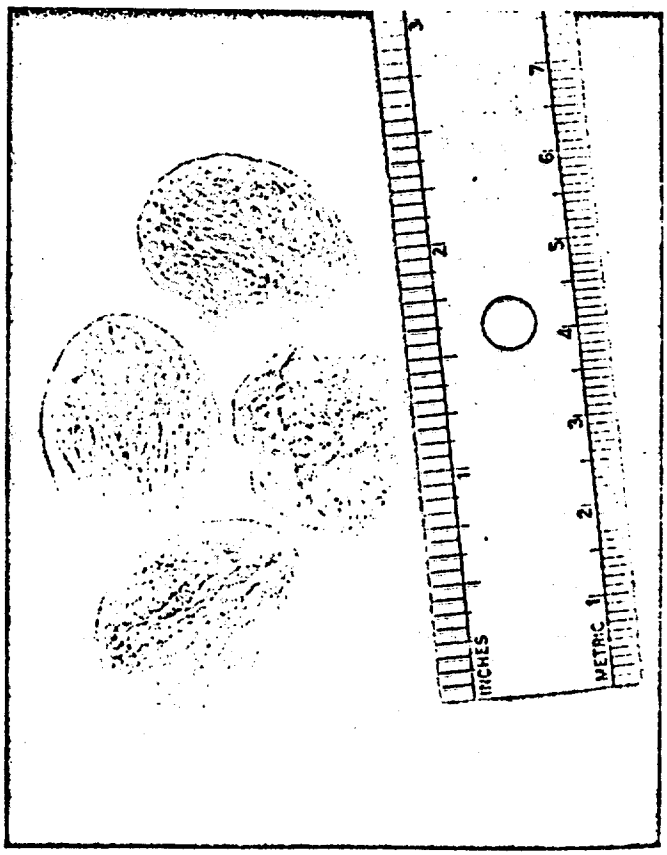
Oil of nutmeg is chemically complex, as shown in the analysis by Power and Salway (3).

Myristicin, $C_{11}H_{12}O_3$, constituting 4 per cent of the oil is interesting as the fraction responsible for many of the pharmacological effects of nutmeg and mace (4).

Chemically, myristicin resembles three other aromatic ether components of Myristica oil; eugenol, isoeugenol, and safrol.

Until recently, both chemists and pharmacologists assumed the "myristicin fraction" of nutmeg oil to be

FIGURE 2



Four nutmegs. One is cut in cross-section to show the internal markings.

a simple substance (myristicin). In 1963, however, Shulgin (6) used chromatographic methods to prove that the myristicin fraction was actually a near-azeotropic mixture of myristicin and elemicin, a closely-related compound. "Consequently," Shulgin wrote, "in assigning chemical and biological properties to the substance as isolated from nutmeg, allowances must be made for this congeneric contaminant".

History of nutmeg as a medicinal agent

In Arabian medicine

Arab physicians seem to have used nutmeg as a drug from the first centuries A.D., although just how they used it is not known. Warburg wrote (1) that *Myristica* was recommended for a variety of disorders in this early period but was taken mainly for diseases of "the digestive organs, from the mouth to the stomach to the intestines, to the liver and spleen, as well as for freckles and skin blotches".

Later Arab physicians referred nutmeg to the class of "warm and dry drugs" and elaborated on its applications. By the 11th century, for instance, the spice was praised for its effect on the kidneys, was used to combat pain, vomiting, and lymphatic ailments, and was even considered aphrodisiac (1). According to Ainslie (7, Vol. I), though, the Arabs were using nutmeg almost solely as a hepatic and tonic by the 19th century. Oddly enough, physicians of the Near East took little notice of mace until the early 1800s when they began to prescribe it as an aphrodisiac and carminative (1).

At the present time, nutmeg is still important in this part of the world. A pharmacologist at the Hebrew University of Jerusalem writes (8):

> "The nutmeg is used by Arabs of Israel and people of its oriental Jewish communities, especially Yemenites, as a drug of their folk medicine, as well as a spice and as an important ingredient in love-potions. It is used against vomiting and to regulate the movements of the bowels; it is good for the liver and for the spleen. It is used in the treatment of tuberculosis, against colds, fever, and, in general, respiratory ailments. It is said to be an antihelminthic and is used for that purpose. It is used against skin diseases like eczema and scabies. It is said to be effective for removing blotches from the face. To increase *potentia virilis* it is pounded well and added to various foods."

In Indian medicine

Frequent references in the Vedas to nutmeg indicate that the ancient Hindus knew of the spice from early times. They described it as warmth-producing, stimulating, and good for digestion and also used it in their medicinal preparations. Martius (9) said that Hindu physicians prescribed it for headache, nerve fevers, cold fevers, foul breath, and intestinal weakness.

In his *Materia Indica* of 1826, Ainslie (7, Vol. I) wrote that nutmeg "is considered by the natives of India as one of their most valuable medicines...." Dymock, in 1883, noted (10) that the Moslems of western India used nutmeg as an aphrodisiac. Burkill, in 1935, stressed (11, Vol. II) nutmeg's importance in Indian tonics for dysentery. According to an adviser in the Indian Ministry of Health, nutmeg is still used medicinally in India (12):

> "It is prescribed as an analgesic in neuritic pains, as a sedative in highly tense nervous states, and as a sedative and anti-spasmodic in asthma. In view of its reaction resembling opium, it is used to give relief in the cough and hemoptysis of tuberculosis. In traditional Indian folk and domestic medicine, nutmeg is used in small quantities to induce hypnotic effect in irritable children. It is also administered as an hypnotic and sedative in epileptic convulsions."

In Western medicine

Medieval European physicians followed exactly the precepts of Arabian medicine. Consequently, they called nutmeg a warm, dry drug and recommended it for all the maladies listed earlier. Warburg wrote (1):

> "The importance of nutmeg as a medicine grew hand in hand with the increase in Indian trade during the middle ages; its use spread from the Arabian Empire over Greece and Italy and soon reached central Europe. Nutmeg gradually became a genuine folk remedy, although it was most important as a major ingredient in medicines prepared according to guild rules."

During the 16th and 17th centuries, Western physicians compiled the writings of earlier authorities on nutmeg. This was the great period of the herbalists, and nearly every herbal contained a summary of nutmeg's virtues (13).

Doctors continued for some time to prescribe *Myristica* for intestinal illnesses, but by 1800 they realized that many of its effects were the same as those of other aromatics. Then, as modern pharmacy developed, older remedies, nutmeg among them, were relegated to positions of lower and lower priority. In summarizing the medicinal uses of the spice in 1897, Warburg wrote (1):

> "Today the employment of nutmeg and mace in medicine is relatively minor. Nutmeg is now used as a stomachic, stimulant, and carminative, especially in

cases of dyspepsia, intestinal catarrh and colic, and as an appetite stimulant, as well as for its ability to control flatulence . . . ."

There is an important omission in the above catalogue of nutmeg uses: sometime later in its history — perhaps as late as the 19th century — nutmeg became known as an emmenagogue and abortifacient. This use has persisted among women into the present century; in fact, Green (14) in 1959 reported the case of a 28-year-old Virginia woman who ate "18.3 g of finely ground nutmeg in an attempt to induce the menses, which had been delayed two days". Some of the older uses of the drug may also be alive in contemporary European and American folk beliefs: McCord (15), for example, cited a 1962 incident in which a 41-year-old South Carolina man, on the advice of a friend, took two whole nutmegs to relieve a skin infection.

Myristica remained official in the United States Pharmacopeia through U.S.P. XIII (1947). Myristica oil was kept on for several more editions, principally as a flavouring agent, but was finally dropped from U.S.P. XVII (1965).

The relevance of medicinal uses of nutmeg to the present discussion of nutmeg as a narcotic is that the toxic properties of *Myristica* must first have been noticed when patients accidentally took overdoses.

Nutmeg poisoning

Early reports

Several European physicians of the 16th and 17th centuries described the symptoms of nutmeg poisoning, and many later references to the toxicity of *Myristica* are traceable to these early observations. In modern writings, the evidence of early commentators is often reduced to the sort of statement that appears in *The Wealth of India* with no amplification (16): "Excessive doses of nutmeg have a narcotic effect; symptoms of delirium and epileptic convulsions appear after 1-6 hours."

There is so much anecdotal material that, considered in its entirety, it makes an impressive case.

With one notable exception, poisoning by mace is not reported in the literature. G. C. Watson, in 1848, published a dramatic account of mace intoxication, characterized chiefly by bizarre alterations of consciousness and hallucinations. Symptoms persisted for three days and, again, resembled those caused by *Cannabis* (17).

Wide use of *Myristica* as a remedy in the Far East would lead one to expect numerous cases of poisoning in that part of the world, but, oddly, no reports on any such mishaps are to be found, and it is not possible to trace to its source the inadequate statement in the 19th edition (1907) of the *Dispensatory of the United States of America* (18):

> "Nutmeg unites to the medicinal properties of the ordinary aromatics considerable narcotic power. In the quantity of two or three drams (7.7 or 11.6 g), it has been known to produce stupor and delirium, and dangerous if not fatal consequences are said to have followed its free use in India."

Intoxication following the use of nutmeg as an emmenagogue or abortifacient

By far the greatest numbers of people poisoned by nutmeg have been women — mostly English and American women of the late 19th and early 20th centuries — who took the spice to bring on menstruation or induce abortion. A great many of these cases appeared in the scientific literature of the period, particularly in British medical journals. Commenting on them in 1962, McCord observed (15):

> "It is interesting that of all the instances reviewed in which nutmeg was taken as an abortifacient, this effort was successful in only one patient. Even in this instance, the role of nutmeg was open to question since the abortion followed the ingestion by a period of a month."

There are many other reports (19), and summarizing all these data, McCord (15) attributed the poisoning symptoms to "a central nervous system depressive effect with periods of stimulation and associated respiratory and cardiovascular difficulties. Occasional case reports have suggested a possible hypersensitivity reaction as illustrated by the presence of facial and periorbital edema with flushing."

Other cases

When children accidentally eat large amounts of nutmeg, serious intoxications occur. The *only* fatality ever attributed to the spice occurred when an eight-year-old boy ate two whole nutmegs, became comatose, and died less than 24 hours later (20).

The apparent "epidemic" of nutmeg poisoning around the turn of the century subsided after the First World War. Cases since then have been rare. Green's 1959 report (14) on a 28-year-old woman, who attempted to bring on menstruation with 18.3 g of ground nutmeg, included the usual physical symptoms as well as profound mental changes that came on eight hours later.

Ample evidence is available on the toxic effects of nutmeg and mace. A puzzling feature of this evidence is its inconsistency; there seems to be no agreement on what symptoms characterize the intoxication or on what doses produce it.

Pharmacology of nutmeg

Early studies

The first pharmacological experiments on nutmeg were performed by van Leeuwenhoek, the Dutch microscopist, around 1676.

As late as 1900, little was known about the action of *Myristica*, largely because researchers could not agree on which component of the seed contained the active principle.

Reviewing the findings of earlier workers, Shulgin in 1963 (22) wrote that the myristicin fraction of nutmeg oil "is strongly suspect of representing the effective toxic factor for cats . . . ." but that it appears "ineffective in duplicating the psychological effects of total nutmeg in man". He then speculated on possible pharmacological activity of other components of the oil:

> "The minor aromatic ethers, eugenol and safrol, have been suggested as possible active components. This seems unlikely, as the amounts ingested from a 5 g nutmeg (0.001 g and 0.003 g respectively) are much below the usual therapeutic levels of these substances (3.0 ml and 0.5 ml respectively). The only component, aside from the myristicin fraction, of the volatile oil from nutmeg that deserves serious consideration as an active agent is the pinenedipentene fraction. Many descriptions of the toxic syndromes of representative terpene medicines parallel the common toxic manifestations of nutmeg (i.e., nausea, cyanosis, stupor, cold extremities, often delirium). [However] actual toxic dosages of oils that are of make-up similar to the hydrocarbon fraction of nutmeg (such as oil of turpentine) are as a rule 20 to 60 times higher than that which would be encountered in nutmeg intoxication."

Shulgin's conclusion is the best summary of our present knowledge of *Myristica*; "As yet, no known pharmacology of any known component of oil of nutmeg can explain the syndrome of the whole nutmeg."

Evidence of narcotic uses of Myristica fragrans

Persistence of rumours

Only one genus in the family *Myristicaceae* is known definitely to be used for narcotic effect. It is not *Myristica* but *Virola*—several species of South American trees whose barks yield a resin that is made into the violently toxic snuff called "yakee" or "paricá" by Indians of the north-west Amazon. Medicine men use yakee for diagnosing disease or prophesying, usually inhaling up to one heaping teaspoonful of the brownish-gray powder. According to Schultes (23), whose paper of 1954 (24) is virtually the only reference on this exotic drug, the users then "fall into a delirous stupor or sleep during which the shouts they emit are interpreted by assistants. That the intoxication can be dangerous is admitted by the medicine men themselves, and the death of one medicine man of the Puinave tribe . . . is laid to the use of *yakee* snuff." Schultes thought myristicin might also be the active principle of *Virola* resin.

In 1964, however, Holmstedt (25) analyzed samples of *Virola* snuff for tryptamines and found 5-methoxy-N,N-dimethyltryptamine to be a major component of this narcotic. He also discovered small amounts of N,N-dimethyltryptamine (DMT) and 5-hydroxy-N,N-dimethyltryptamine (bufotenin). The pharmacology of 5-methoxy-N,N-dimethyltryptamine is poorly understood, but both DMT and bufotenin are known psychotomimetic drugs.

These few facts on *Virola* are more conclusive than most information available on the narcotic use of *Myristica*. It is not yet possible to say how widely nutmeg is used to induce alterations of consciousness. The medical literature is of little help in providing answers because nearly all the reported cases of nutmeg intoxication have resulted from accidental ingestions or from overdoses taken as remedies.

At the same time, there is an impressive amount of anecdotal evidence suggesting that many people throughout the world consume nutmeg as a psychoactive agent. One hears persistent rumours, for instance, that *Myristica* serves as a narcotic in the Orient, that it is commonly taken by prison inmates, and that it has become a popular hallucinogenic drug among bohemians and students in the United States.

Is nutmeg used as a narcotic in the East ?

There is reason to believe that Indian folk practices embrace the use of nutmeg as a narcotic, though certainly not on as wide a scale as drug-takers in the U.S. seem to think. An obscure clue is one of the synonyms for nutmeg in Ayurveda: *Mada shaunda*, meaning "narcotic fruit". Dr. C. Dwarakanath, of the Indian Ministry of Health, has informed me (12) that "*M. fragrans* is generally chewed together with betel for the slight excitement it gives. It is also consumed orally with a view to stimulating the libido. *Mada shaunda* refers to its narcotic action." He adds that "in certain parts of southern India, *M. fragrans* is mixed with tobacco snuff and used".

A story frequently encountered is that *Cannabis* devotees will turn to nutmeg when they cannot get hemp. Again, there is only one bit of published evidence—two lines from Bamford's *Poisons* (4) of 1951: "Within the last few years, partly owing to the difficulty in obtain-

ing hashish, it has become the practice in Egypt to substitute powdered nutmeg. In sufficiently large doses this produces symptoms similar to those of hashish intoxication and the effects may even be much more severe." Unfortunately, no further information on this subject is available from Egyptian governmental agencies, and no other writer has confirmed Bamford's observation.

Is nutmeg used as a narcotic in prisons ?

Most stories in circulation in the US about nutmeg as a narcotic concern its use in prisons. If they are true, nutmeg and mace would seem to be serious problems in correctional institutions. An officer of the US Bureau of Prisons has dismissed this idea as an exaggeration (26). However a short article on page 22 of the Chicago *Sun-Times* of March 3, 1961, headlined "Nutmeg Costs a County Jail Guard His Job", proves at least that people in some prisons are familiar with *Myristica*.

The Director of the Addiction Research Center at the US Public Health Service Hospital in Lexington, Kentucky, W. R. Martin, has said (27) that many patients he has seen believe mace and, especially, nutmeg to have "stimulating effects," usually because they have heard the prevalent rumours. He adds that patients rarely volunteer information on *Myristica* experiences and that the use of nutmeg or mace is far from universal; but he estimates that about one out of ten Lexington patients will admit having tried occasional self-experiments with these spices. Most persons who have used *Myristica*, he feels, do not attach much importance to it until they are confined within institutions. There is substantial confirmation of Martin's impressions in an article by Weiss (28) describing a study on the "Hallucinogenic and Narcotic-like Effects of Powdered Myristica" conducted at the New Jersey State Prison, Trenton, in 1960. Weiss noted that many commercial and medicinal substances were used covertly by prisoners to "escape from one's self and the depressing, immediate surroundings," and he wrote: "Powdered myristica . . . is included among the inmates' repertory of alleged euphoria-inducing drugs."

Weiss studied ten male inmates of the prison, most of whom had had previous experience with marihuana and other drugs. The minimum amount of ground nutmeg any man ingested was two to three tablespoonfuls, and one had once taken two cups of the spice as a single dose (apparently without unusually severe reaction or permanent systemic damage). The drug was always taken orally, usually stirred into hot liquids. Most of the subjects compared nutmeg to marihuana. One said: "It made me feel light, like with a marihuana cigarette" though another explained: "One reefer (i.e., a marihuana cigarette) will get you three times as high as nutmeg; it slows your actions down."

Weiss concluded that:

"Doses of two to three tablespoonfuls of powdered nutmeg tended to narcotize the subjects against the unpleasant experience of incarceration, without a blurring of the boundaries between the self and the outer world. The effects were considered to be essentially similar to those of marihuana, although comparisons with heroin and alcohol were also cited. In most instances, a feeling of being transported aloft was experienced accompanied by a feeling of drowsiness in some cases and excitement or stimulation in others . . .

"Symptoms of physiological addiction were not reported. No positive correlation was obtained between the 'light-feeling' and the mood experience. Nor did the mood experience, be it gay or melancholy, for example, serve as an index to whether inmates would prefer to promote social contacts or encyst themselves from them. It was also reported, in most instances, that the ability to enjoy certain pastimes was enhanced. In all instances of recall, thirst was increased, and hunger was largely diminished or unaffected. The various side effects reported were nausea, abdominal spasm, vomiting, constipation, tachycardia, insomnia, and drowsiness.

"Two cases of acute brain syndrome with psychotic reaction due to nutmeg intoxication were reported. Each of the two subjects had chronically ingested powdered nutmeg over a long period . . . . Aside from the case of nutmeg poisoning, the hallucinogenic effects reported were transitory and of brief duration."

Nutmeg has since been banned from the New Jersey State Prison kitchen.

Do bohemians and students use nutmeg as a narcotic ?

An undergraduate at a well-known US college gives me this information:

"I recently had a visit from a 'beatnik' acquaintance who smokes marihuana frequently and has tried other drugs. I asked him if he had heard that nutmeg was a narcotic, and he replied, 'We've known about that for years.' He explained that he and many of his friends had tried nutmeg several times, taking it both as a snuff and by mouth. They did not think it was very good, however, because 'you either get very sick or have a horrible experience.' He said that people who like to 'blow pot' (i.e., smoke marihuana) sometimes take nutmeg when they can't get marihuana."

Since all aromatic spices contain volatile compounds that affect the central nervous system, these alleged properties of familar substances are plausible. It is interesting that the narcotics-user believes different spices capable of providing different experiences — nutmeg can be " horrible " or ginger " dangerously potent ". Pharmacologists agree that psychological expectations largely determine the form of a narcotic intoxication. Consequently, a person expecting horrible effects from nutmeg may well experience them. This may explain why women poisoned accidentally by nutmeg merely become stuporous, while prisoners have predominantly pleasant times under *Myristica*; prisoners take the spice to escape reality, and they expect it to be much like *Cannabis*.

A growing problem in the United States is the use of hallucinogenic drugs like LSD and marihuana by young persons, especially students in secondary schools and universities (30). There is some evidence that these people also try self-experiments with nutmeg.

Callaway (29) maintains that jazz musicians " have known about nutmeg for some time but will not discuss it except with friends ". Most bohemians, addicts and students who try the spice probably are equally secretive.

Experimentation with nutmeg may be widespread on American university campuses. In the summer 1964 issue of a University of Mississippi student magazine, an article titled " Nutmeg Jag " described a nutmeg party attended by eight persons.

Like prisoners, students who use marihuana may often turn to nutmeg when cut off from supplies of *Cannabis*. But it would seem that marihuana is obtainable with minimum difficulty around most US universities today, and there is no doubt students (like prisoners) prefer *Cannabis* to *Myristica*.

As a final word on the uses of nutmeg, there is the report of Truitt *et. al.* (21) that the practice of taking this spice to produce " a syndrome comparable to alcoholic inebriety " is " not uncommon among alcoholics who are deprived of alcohol ".

Psychopharmacology of nutmeg: A brief note

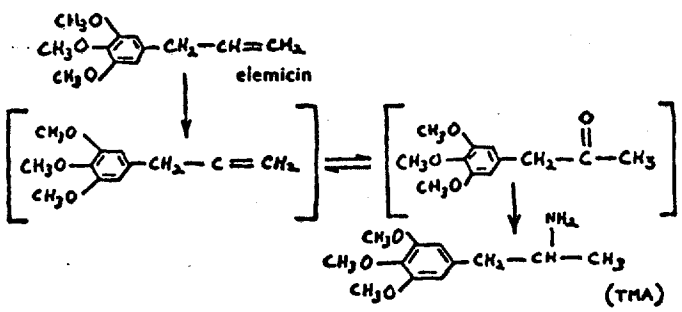
Speculation on the psychopharmacology of nutmeg must be cautious, since, as Shulgin has said (22), " the inability to assign to a single component of nutmeg the role of being the toxic factor makes a discussion of the mode of action, by definition, totally theoretical ".

None the less, a few findings are interesting. Truitt and a new group of researchers in 1963 pointed out (31) " a degree of structural resemblance between the chemical formula for myristicin and those of certain sympathomimetic amines ". This similarity, together with nutmeg's stimulant action, suggested that myristicin and nutmeg may act as central monoamine oxidase (MAO) inhibitors. To test this hypothesis, synthetic myristicin and nutmeg oil concentrate were given to rats, and MAO inhibition was established by measuring potentiation of tryptamine convulsions. Controls were run with two potent known MAO inhibitors: tranylcypromine and iproniazid. By these methods, myristicin was shown to produce effects less potent than but parallel to those of the reference drugs. Myristicin was also found to antagonize reserpine ptosis and to increase brain 5-hydroxytryptamine — both of which are changes induced by other MAO inhibitors.

The authors emphasized that this was mere circumstantial evidence, but they felt that nutmeg and myristicin probably were mild MAO inhibitors. Compared to other such compounds, their toxicity is quite low. The authors cited preliminary work with schizophrenic and depressed patients in whom daily administration of ground nutmeg caused " improvements ". They concluded: " Further study is recommended for more direct evidence of nutmeg and myristicin as enzyme in hibitors and for their utility as anti-depressant drugs."

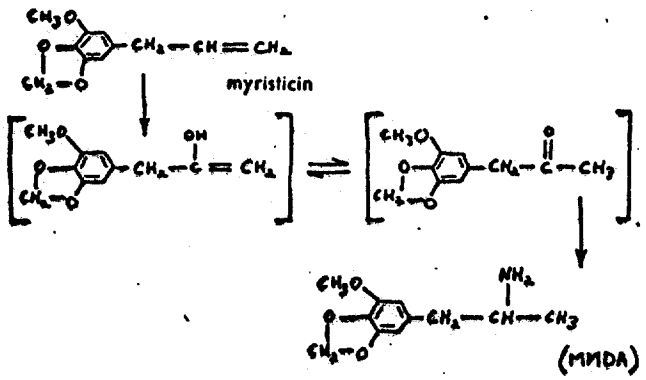
Shulgin, who has tried to work out the biochemistry of nutmeg's hallucinogenic action, has assumed (22) for the moment that the myristicin fraction of the oil (with its more than 25 per cent content of elemicin) is, indeed, the active principle. He has noted that the metabolism of the aromatic ethers found in essential oil is " virtually unknown " except for a detoxication mechanism by which safrol is converted to piperonylic acid. This reaction indicates a capacity to oxidize an olefinic side chain. Shulgin has suggested that, if this degradative process is " applicable to myristicin, or especially to elemicin, a theoretical intermediate, a vinyl alcohol, could undergo transamination producing the known psychotomimetic drug, 3,4,5-trimethoxy amphetamine (TMA) ". The recent description of the new synthetic hallucinogen — 3-methoxy-4, 5-methylenedioxy amphetamine (MMDA) — which might be derived by an analogous process from myristicin, itself, is even more suggestive of a psychotropic function for this component of nutmeg (fig. 3*b*) (5).

FIGURE 3a



Possible production of a known psychotomimetic agent from elemicin.

FIGURE 3b



Possible production of a known psychotomimetic agent from myristicin.

Thus far, human pharmacological data are inadequate to support the contention that myristicin is psychoactive or that it is an active principle of whole nutmeg. Shulgin has written (22): ". . . some combination of factors in total nutmeg is capable of producing a psychotropic response: the structure of elemicin or myristicin wanting only an ammonia molecule to become a recognized mental agent must be accepted as at least an intriguing coincidence."

Conclusions

The seeds and arils of *M. fragrans* have powerful narcotic properties. In man, they have frequently caused serious but almost never fatal intoxications. Most Westerners are ignorant of these toxic properties and know nutmeg and mace only as flavouring agents.

Both spices are used as narcotics, probably by significant numbers of people, although information on this use of *Myristica* is scarce. When taken deliberately as psychotropics, nutmeg and mace often cause reactions quite unlike those described in classical accounts of *Myristica* poisoning and much more like experiences with *Cannabis* or other hallucinogenic drugs. Law enforcement officers and governmental authorities are not aware of the importance of nutmeg as a narcotic.

Thorough investigation of the history, sociology, and biochemistry of *Myristica* narcosis would be most valuable.

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Nutmeg Poisoning

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THE PRESENT-DAY use of nutmeg (Myristica fragrans) is confined largely to exploitation of its properties as a flavoring agent. In the past it has been used medicinally as an aromatic stimulant, a carminative and a narcotic. In England and India it has been used widely by the laity as an emmenagogue and an abortifacient, and from these uses came many reports of nutmeg poisoning in the early literature. During the last half-century, nutmeg poisoning seldom has been reported, and only limited information is available concerning the physiologic and biochemical effects of this particular toxic state.

REVIEW OF THE LITERATURE

One of the earliest cases of nutmeg poisoning was recorded by Lobelius in 1576.[1] In 1832 Purkinge[2] dramatically illustrated the toxic effect of this kernel by self-administering three nutmegs and producing a narcosis which progressed to stupor. In 1903 Wallace[3], in a review of nutmeg poisoning, reported 25 cases from the world literature. Although one of the persons concerned died[4], those in the remaining 24 cases recovered promptly without residual effect. Since Wallace's review a limited number of cases of nutmeg poisoning have been noted in the literature. These more recent reports are brief, clinical description is meager and laboratory studies are not included. However, they are of interest and are presented in detail below.

Case 1. Reported by Bartlett[5]—A young woman took one ground nutmeg* in a glass of hot beer in an attempt to induce abortion. Four hours later she became restless and excited. She complained of difficulty in breathing, tightening of the throat and stiffening of the entire body. In addition, she noted headache, giddiness and pain in the stomach. Examination revealed rapid respiration, flushed face, a pulse of 130 beats per minute, and a temperature of 98.6° F. The pupils were dilated but reacted normally to light, and accommodation was satisfactory. The knee reflexes were exaggerated. She was treated symptomatically and slept heavily through the night. The next day she felt drowsy and giddy. Abortion did not occur.

Case 2. Reported by Hammond[6]—A 34-year-old woman took a crushed nutmeg in water for menstrual irregularity. Three hours later she became giddy, was unable to stand and complained of feeling queer. She noted the sensation of weight on her chest, and vomiting occurred. Examination revealed her to be conscious but in a state of collapse. She was pale; her extremities were cold and clammy. The pulse was 98 beats per minute. The respiration was shallow, rapid and irregular, and the pupils appeared to be normal. Therapy consisted of the use of strychnine, whisky and general supportive measures. The next day she was well, complaining only of weakness.

Case 3. Reported by Hamilton[7]—A woman took one nutmeg in an attempt to induce abortion. Symptoms of restlessness, giddiness and a sense of impending death developed. She then went into a state of collapse. Examination revealed cyanosis of the lips, fingernails and coldness of the extremities. The face was flushed and there was choreic spasm of the lower jaw and larynx. Prompt recovery followed, although abortion took place one month later.

Case 4. Reported by Wilkinson[8]—A 23-year-old woman took one ground nutmeg with a glass of stout in an attempt to induce abortion. Four hours later intense headache, abdominal pain and giddiness developed, and unconsciousness ensued. She was admitted to a hospital seven hours after taking the nutmeg. At this time she complained constantly of her head, and was restless and excited. She was unable to answer questions. Examination revealed her face to be flushed; her pulse was 120 beats per minute and the pupils were normal. The abdomen was reported as tender, especially in the area of the descending colon. There was no rigidity. The next day the pain and headache had disappeared, but some giddiness remained. Abortion did not occur.

Case 5. Reported by Johnson[9]—A woman took one large grated nutmeg in an attempt to produce abortion. Ten hours later she complained of restlessness, giddiness and a great fear of impending death. She became delirious and described her head as being many times its normal size. Vomiting occurred sev-

From the Medical Service, Community Memorial Hospital, South Hill.
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*One average-size nutmeg weighs approximately 5 gm.

eral times. Examination revealed redness and edema of her face and eyelids. Cyanosis of the lips and nail beds was noted. Her temperature was 103°F. Treatment consisted of the administration of quinine and aperients. The patient returned to work in five days. Abortion did not occur.

Case 6. Reported by Gibbins[10]—A 22-year-old man ate a milk pudding containing one quarter of a moderate-sized nutmeg. Within a few minutes he noted flushing of the face, with itching and bleeding of the nose. This was followed by abdominal pain and vomiting. He became unconscious and remained in this condition for a half-hour. Examination revealed swelling of the lips and eyelids. The pupils were contracted. The extremities were cold and appeared cyanotic. The pulse was rapid and faint. The heart was pounding and irregular. A half-hour after the initial examination the face was still swollen and itched slightly. The cyanosis subsided and was replaced by a flush. All symptoms disappeared except a slight drowsiness. The next day he was asymptomatic.

Case 7. Reported by Pitter[11]—A woman took a whole grated nutmeg in a wine glass of gin in an attempt to produce abortion. One hour later she was found in a state of collapse, muttering unintelligibly. Examination revealed her pupils to be dilated, but reacting feebly to light. Her extremities were clammy and her pulse was barely perceptible. After gastric lavage she remained in a muttering delirium throughout the night, and slept heavily the next day. She awoke on the second day, apparently recovered. Abortion followed.

Case 8. Reported by Reekie[12]—A woman took one ground nutmeg on an empty stomach for menstrual irregularity. Five hours later she was in a state of collapse. Examination revealed that her skin and extremities were cold. The face was flushed and mottled. The temperature was 95°F. The pulse was 50 beats per minute and was feeble. Respiration was 30 to 40 per minute, and every second breath was a sigh. Treatment consisted of the use of strychnine and ammonium carbonate, as well as spirits of ether and chloroform. The patient's pulse and temperature returned to normal in 24 hours, and she appeared to be fully recovered.

It is apparent from these reports, and those of Wallace, that only limited observation on nutmeg poisoning is available. Therefore, it was felt that a detailed report of such a case from the author's experience would be of interest.

REPORT OF A CASE

A 28-year-old married colored woman was admitted to the Community Memorial Hospital in South Hill, Virginia, in a semistuporous condition. The medical and psychiatric history up to this time had been normal. She had been married nine years and had experienced two uneventful pregnancies. At 10 p.m. the night before admission to the hospital she had eaten 18.3 gm. of finely ground nutmeg in an attempt to induce the menses, which had been delayed two days. She had slept soundly without disturbance until 5:30 a.m. the next day. At that time she had been awakened by a burning sensation in the lower part of the abdomen and an overwhelming feeling of impending death. She vomited once. Her legs felt as if they were asleep and she complaining of feeling "funny all over". She then had become completely disoriented, with episodes of wild screaming and purposeless thrashing of the arms and legs. Coordination appeared absent. Interspersed in this period of disorientation were brief moments of lucidity during which she seemed to be aware of her surroundings. From the time of her awakening at 5:30 a.m. until 9:30 a.m., when she was seen by her local physician, there were three intervals of lucidity, each lasting approximately 10 minutes. The remainder of this time she was delirious and in a state of excitement and agitation.

This patient was admitted to the hospital at 11:30 a.m., approximately 13 hours after she had taken the nutmeg. On admission she was in a semistuporous state. She could be aroused to talk, but would immediately return to the semistuporous condition. The skin was cool but not clammy. There was no cyanosis. Blood pressure initially was 100 systolic and 50 diastolic, expressed in millimeters of mercury. The pulse rate was 100 beats per minute, the temperature 98°F. and respiration was 24 per minute. The pupils were small and reaction to light was not visible. The thorax was clear to auscultation, palpation and percussion. The heart was not enlarged and there were no murmurs. The abdomen was not tender and the liver, spleen and kidneys were not palpable. The extremity reflexes were absent. Pelvic examination revealed evidence of beginning menstrual flow. Results of rectal examination were negative. The erythrocyte count was 3,710,000 per cubic millimeter of blood and the value for hemoglobin was 68%. The leukocyte count was 7,400 per cubic millimeter of blood, 87 per cent of the cells being segmented neutrophils and 13 per cent lymphocytes. Results of the serologic tests of

the blood was negative. Specific gravity of the urine was 1,020; the hydrogen-ion concentration was acid. Albuminuria was graded 2+; there was neither sugar nor bile. The value for carbon dioxide was 14.9 mEq. per liter of plasma. The content of sodium was 126 mEq. per liter of serum and of chlorides, 108 mEq. per liter of plasma. The concentration of potassium was 3.8 mEq. per liter of serum. The value for nonprotein nitrogen was 47 mg. per 100 cc. of serum.

The patient remained in a semistuporous condition for 12 hours after her admission. She then began to experience episodes of wild excitement, with loud screaming and manifestations of a fear of impending death. She continued to be subjected to episodes of excitement for two hours, during which time restraints were needed. During the remainder of the second day she was restless, but essentially quiet. During the third and fourth day of hospitalization she slept much and complained constantly, while she was awake, of a generalized feeling of numbness and dizziness.

Laboratory investigation on the third day revealed the value for nonprotein nitrogen to be 36.5 mg. per 100 cc. of serum. The specific gravity of the urine was 1.020; the hydrogen-ion concentration was acid. There was no albuminuria, sugar or bile. The result of the bromsulphalein test was 10.5 per cent retention of dye in 30 minutes. The direct bilirubin was .05 mg. per 100 cc. of serum; the total bilirubin was 0.35 mg. per 100 cc. of serum. The reaction of the cephalin flocculation test was graded negative. On the fourth day of hospitalization the result of a phenolsulfonphthalein test was recorded as 77 per cent excretion of the dye in 2 hours. Urine obtained during this test had a specific gravity of 1.002; there was no sugar, albumin or bile. Total proteins amounted to 6.1 gm. per 100 cc. of serum, with 4.5 gm. of albumin and 1.6 gm. of globulin. The prothrombin time was recorded as 100 per cent. A transthoracic procedure to obtain hepatic tissue for biopsy was done at this time. Microscopic sections of the tissue showed no evidence of fatty infiltration or hepatic-cell necrosis.

On the fifth hospital day the patient complained of nausea, dizziness and generalized numbness. At intervals throughout this day she became restless and noisy, and frequently expressed a fear of imminent death. These symptoms persisted intermittently with decreasing frequency and intensity through the sixth day. In between these episodes she appeared essentially normal.

She was discharged on the seventh hospital day. Laboratory studies at that time revealed retention of bromsulphalein dye to be 8 per cent in 30 minutes. The specific gravity of the urine was 1.024. There was a trace of albuminuria, but no sugar or bile. The hydrogen-ion concentration was acid. The direct bilirubin was 0.15 mg. per 100 cc. of serum and the total bilirubin was 0.95 per 100 cc. of serum.

The patient returned for follow-up studies 10 days after discharge. At that time the results obtained from a complete blood count, urinalysis, and cephalin flocculation, bromsulphalein and serum bilirubin tests and determination of nonprotein nitrogen remained essentially unchanged from those recorded at previous procedures. She reported that she was without symptoms of any kind. Because of the limited information available concerning nutmeg poisoning, no specific therapy was given in this case except for intramuscular injections of promazine hydrochloride during periods of excitement.

COMMENTS

On the basis of data in this case and in those noted from the literature, it is apparent that nutmeg taken in moderate quantities may produce a serious toxic state and possibly death. To obtain a clearer understanding of the problem, the pharmacological and chemical features of nutmeg will be discussed as well as the clinical syndrome resulting from ingestion of the substance in toxic amounts. Because of the almost total absence of interest in this subject in the recent literature, all information concerning the properties of nutmeg have come from a limited number of early studies.

Pharmacologic Aspects. Wallace reported that the toxic factor of nutmeg is confined entirely to the volatile-oil component. He administered this oil (0.4 gr. per kilo gram of body weight) to cats by stomach tube and produced a striking clinical response. Within 10 minutes he noted restlessness, excitement and excessive salivation. These signs were followed by a period of quiet associated with incoordination and staggering. Mydriasis usually was noted at this time. The reflexes became weakened and a condition of semiconsciousness supervened during which respiration was labored and feeble. In some animals unconsciousness deepened, respiration became labored and feeble and death occurred 8 to 12 hours after ingestion of the oil. Usually, however, after the stage of unconsciousness had developed, gradual improvement occurred, and approximately 15 hours after the oil had been given

the animal appeared to return to normal. This improvement generally was temporary; the animal then gradually weakened and within 36 to 72 hours after administration of the oil coma developed and death followed. Necropsy of these animals consistently showed advanced fatty degeneration of the liver.

Dale[13] and Jurss[14], using myristicin, a constituent of the volatile oil, were able to reproduce in animals symptoms identical to those caused by the administration of the nutmeg or the volatile oil of nutmeg. They concluded that myristicin is the toxic factor in nutmeg. Necropsy of their animals showed changes in the liver similar to those described by Wallace.

Chemical Aspects. Nutmeg is known to contain from 5 to 15 per cent volatile oil, 25 to 40 per cent fixed oil and 5 to 15 per cent of ash. The remainder is starch, fiber and water.[15] Power and Solway[16], in an analysis of this volatile oil, found that 4 per cent was myristicin. They noted that the formula for myristicin is $C_{11}H_{12}O_3$ and it is 5-allyl-1 methoxy-2,3,-methylenedioxybenzene. Further analysis of the volatile oil revealed 80 per cent to be dextrocamphene and dextropinene, with 8 per cent dipentene. Also noted were small amounts of eugenol, iso-eugenol, lenalool, borneol, terpinol, geraniol and safrol. In addition, they isolated limited amounts of free myristic acid and traces of esters of this and other fatty acids.

Clinical Aspects. It is apparent from this case and those previously reported that nutmeg in doses of 5 gm. or more will produce a characteristic clinical syndrome. From one hour to seven hours after the ingestion of nutmeg, symptoms of a burning, midabdominal pain, with or without vomiting, may occur. Restlessness, giddiness and excitement may be noted. Frequently a fear of impending death is reported and often there is a compaint of a sensation of a heavy weight on the chest. During the next 10 hours drowsiness progressing to stupor may develop. However, the patient can be aroused; if this is done, delirium and agitation ensue; then the patient sinks again into stupor. Some patients may not manifest the early symptoms of toxicity but may display only the late narcotic effect. As a rule recovery is complete within 24 hours. However, large doses of nutmeg may prolong recovery, and periodic outbursts of excitement with delirium may continue for several days or more.

Significant physical findings may include a decrease in blood pressure, with cyanosis and shock. In addition, there may be rapid respiration, tachycardia, dilation of the pupils and decreased-to-absent peripheral reflexes.

Several of the early reports suggest that some patients may exhibit, in addition to the usual symptoms and signs, an acute allergic response to nutmeg. This response is manifested by edema of the eyelids, with marked flushing and itching of the face. There also may be an evaluation of temperature. These symptoms of an allergic reaction apparently subside quickly.

Some of the laboratory findings in the case I have reported are not entirely understood. Since previous studies did not contain laboratory reports, the chemical determinations recorded in the present case are difficult to evaluate. In this case acidosis was noted with depression of the values for sodium and potassium. The content of chloride was within the normal range.

On the basis of the experimental work on cats by Wallace, Dale and Jurss, it appeared that fatty dengeration of the liver was the end result of toxic doses of the volatile oil or the derivative thereof: myristicin. However, in the case reported herein serial studies of hepatic function as well as biopsy of tissue from the liver revealed no evidence of damage to that structure.

Studies of renal function revealed an initial slight elevation of the value of nonprotein nitrogen as well as albuminuria of grade 2+, although the output of urine during the first 24 hours was normal. The value for nonprotein nitrogen returned to normal the next day and subsequent urinalyses disclosed occasional traces of albumin. It seems probable that in the case presented herein nutmeg produced a transient toxic effect on the kidney.

SUMMARY

A case of nutmeg poisoning has been presented, with a review of the literature. The toxic factor of nutmeg is known to be myristicin, a constituent of the volatile oil of nutmeg.

Nutmeg in doses of 5 gm. or more produces a marked depressant action on the central nervous system as well as a less prominent stimulating effect. The clinical course may be severe, with coma, shock and acidosis as prominent features.

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Myths About Pregnancy

If you eat ice cream, the baby inside of you will catch cold.

If you want a boy, eat peanuts and alkalies; for a girl, eat sweets and acids.

If you have heartburn, the baby will have lots of hair.

These are just some of the old wives' tales that plague pregnant women. They exist because occasionally coincidence seemingly makes one come true, according to an article in the August Today's Health, published by the American Medical Association.

Mrs. Joan S. Pollack, a University City, Mo., mother, pointed out that the major hazard in passing on such tales is that the pregnant woman seems to be especially imaginative. She is concerned with protecting her child and is only too likely to be scared by the myths.

Among the myths are:

—Broad-hipped women have easier deliveries than those with narrow hips. This belief can't hurt, even though it is the internal, not external, measurements that determine ease of delivery.

—If you eat lobster, you will mark the baby. To which, Mrs. Pollack replied, "If I drink milk, will my baby look like a cow?"

—The majority of markings are supposedly due to happenings late in pregnancy, yet the fetus formed early in pregnancy.

Not only can a mother never mark her baby a detrimental fashion, but she will only bore her if she listens to piano recitals 10 hours a day hopes of influencing her child to be a brilliant pia

—It is safer to be born in the seventh month th the eighth month of pregnancy. This stems from ancient Greek belief that a baby tried to get out ing the seventh month and if it was strong it ceeded. If it failed and tried again the next mo it would be so tired it would die of exhaustion.

The truth is that every day a baby remains in the mother—up to the normal term—it gets stron and healthier and more likely to survive.

—It is lucky for a baby to be born with a ca The Roman midwives sold cauls for good luck sailors and travelers. The caul is caused when membranes surrounding the baby are abnorma tough and instead of rupturing, remain intact are pulled down with the advancing head.

Several other myths about the labor are: the ba head sinks to the pelvis at the dark of the m change of moon starts labor; girls make harder than boys; each person the mother talks to after starts prolongs the pains; if a woman has a la mouth, labor will be easy; mothers must not bre deeply during labor since it holds the baby ba

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NUTMEG POISONING

Robert C. Green Jr., M.D., Winchester, Va.

The present-day use of nutmeg (Myristica fragrans) is confined largely to exploitation of its properties as a flavoring agent. In the past it has been used medicinally as an aromatic stimulant, a carminative, and a narcotic. In England and India it has been used widely by the laity as an emmenagogue and an abortifacient, and from these uses came many reports of nutmeg poisoning in the early literature. During the last 50 years nutmeg poisoning has seldom been reported, and only limited information is available concerning the physiological and biochemical effects of this particular toxic state.

Review of the Literature

One of the earliest cases of nutmeg poisoning was recorded by de Lobel in 1576.[1] In 1832 Purkinje [2] dramatically illustrated the toxic effect of this kernel by consuming three nutmegs, producing a narcosis which progressed to stupor. In 1903 Wallace,[3] in a review of cases of nutmeg poisoning, reported 25 from the world literature. Although one of the patients concerned died,[4] the remaining 24 recovered promptly without residual effects. Since Wallace's review a limited number of cases of nutmeg poisoning have been noted in the literature.[5] These more recent reports are brief; the clinical descriptions are meager and laboratory studies are not included. It is apparent from these reports and those of Wallace that only limited observation of nutmeg poisoning is available. Therefore, it was felt that a detailed report of such a case from my experience would be of interest.

Report of a Case

A 28-year-old woman was admitted to the Community Memorial Hospital in South Hill, Va., in a semistuporous condition. The medical and psychiatric history up to this time had been normal. She had been married nine years and had experienced two uneventful pregnancies. At 10 p. m. on the night before admission to the hospital she had eaten 18.3 Gm. of finely ground nutmeg in an attempt to induce the menses, which had been delayed two days. She had slept soundly without disturbance until 5:30 a. m. the next day. At that time she had been awakened by a burning sensation in the lower part of the abdomen and an overwhelming feeling of impending death. She vomited once. Her legs felt as if they were asleep and she complained of feeling "funny all over." She had then become completely disoriented, with episodes of wild screaming and purposeless thrashing of the arms and legs. Coordination appeared absent. Interspersed with this disorientation were brief moments of lucidity during which she seemed to be aware of her surroundings. From the time of her awakening at 5:30 a. m. until 9:30 a. m., when she was seen by her local physician, there were three intervals of lucidity, each lasting about 10 minutes. The rest of this time she was delirious and in a state of excitement and agitation.

This patient was admitted to the hospital at 11:30 a. m., about 13 hours after she had taken the nutmeg. On admission she was in a semistupor. She could be aroused to talk, but would immediately return to the semistuporous condition. The skin was cool but not clammy. There was no cyanosis. Blood pressure initially was 100/50 mm. Hg, pulse rate 100 and respirations 24 per minute, and temperature 98 F (36.7 C). The pupils were small and reaction to light was not visible. The thorax was clear to auscultation, palpation, and percussion. The heart was not enlarged and there were no murmurs. The abdomen was not tender and the liver, spleen, and kidneys were not palpable. The extremity reflexes were absent. Pelvic examination revealed evidence of beginning menstrual flow. Results of rectal examination were negative. The erythrocyte count was 3,710,000 per cubic millimeter, and the hemoglobin value was 6.8 Gm. per 100 cc. The leukocyte count was 7,400 per cubic millimeter, with 87% segmented neutrophils and 13% lymphocytes. Results of serologic tests were negative. Specific gravity of the urine was 1.020; the hydrogen-ion concentration was acid. Albumin content of urine was graded 2+; there was neither sugar nor bile. The carbon dioxide–combining power was 14.9 mEq. per liter of plasma. The serum sodium content was 126 mEq. per liter and plasma chloride content, 108 mEq. per liter. The serum potassium concentration was 3.8 mEq. per liter. The value for serum nonprotein nitrogen was 47 mg. per 100 cc.

The patient remained in a semistupor for 12 hours after her admission. She then began to experience episodes of wild excitement, with loud screaming and manifestations of a fear of impending death. She continued to be subjected to episodes of excitement for two hours, during which time restraints were needed. For the remainder of the second day she was restless but essentially quiet. During the third and fourth days of hospitalization she slept much but complained constantly, while awake, of a generalized feeling of numbness and dizziness.

Laboratory investigation on the third day revealed the value for serum nonprotein nitrogen to be 36.5 mg. per 100 cc. The specific gravity of the

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urine was 1.020; the hydrogen-ion concentration was acid. There was no albumin, sugar, or bile in the urine. The result of the sulfobromophthalein tolerance test was 10.5% retention of dye in 30 minutes. The direct serum bilirubin content was 0.05 mg. per 100 cc.; total bilirubin was 0.35 mg. per 100 cc. The reaction of the cephalin flocculation test was graded negative. On the fourth day of hospitalization the result of a phenolsulfonphthalein test was recorded as 77% excretion of the dye in two hours. Urine obtained during this test had a specific gravity of 1.002; there was no sugar, albumin, or bile. Total serum proteins amounted to 6.1 Gm. per 100 cc., with 4.5 Gm. of albumin and 1.6 Gm. of globulin. The prothrombin time was recorded as 100%. A transthoracic procedure to obtain hepatic tissue for biopsy was done at this time. Microscopic sections of the tissue showed no evidence of fatty infiltration or hepatic cell necrosis.

On the fifth hospital day the patient complained of nausea, dizziness, and generalized numbness. At intervals throughout this day she became restless and noisy and frequently expressed a fear of imminent death. These symptoms persisted intermittently with decreasing frequency and intensity through the sixth day. Between these episodes she appeared essentially normal.

She was discharged on the seventh hospital day. Laboratory studies at that time revealed retention of sulfobromophthalein to be 8% in 30 minutes. The specific gravity of the urine was 1.024; there was a trace of albumin, but no sugar or bile. The hydrogen-ion concentration was acid. The direct serum bilirubin content was 0.15 mg. per 100 cc., and the total bilirubin was 0.95 per 100 cc.

The patient returned for follow-up studies 10 days after discharge. At that time the results obtained from a complete blood cell count; urinalysis; cephalin flocculation, sulfobromophthalein, and serum bilirubin tests; and determination of nonprotein nitrogen remained essentially unchanged from those recorded at previous procedures. She reported that she was without symptoms of any kind. Because of the limited information available concerning nutmeg poisoning no specific therapy was given in this case, except for intramuscular injections of promazine hydrochloride during periods of excitement.

Comment

On the basis of the data in this case and in those noted from the literature it is apparent that nutmeg taken in moderate quantities may produce a serious toxic state and possibly death. To obtain a clearer understanding of the problem the pharmacological and chemical features of nutmeg will be discussed, as well as the clinical syndrome resulting from ingestion of the substance in toxic amounts. Because of the almost total absence of interest in this subject in the recent literature all information concerning the properties of nutmeg have come from a limited number of early studies.

Pharmacological Aspects.—Wallace reported that the toxic factor of nutmeg is confined entirely to the volatile oil component. He administered this oil (0.4 grains [24 mg.] per kilogram of body weight) to cats by a stomach tube and produced a striking clinical response. Within 10 minutes he noted restlessness, excitement, and excessive salivation. These signs were followed by a period of quiet associated with incoordination and staggering. Mydriasis was usually noted at this time. The reflexes became weakened and a condition of semiconsciousness supervened, during which respiration was labored and feeble. In some animals unconsciousness deepened, respiration became labored and feeble, and death occurred 8 to 12 hours after ingestion of the oil. Usually, however, after the stage of unconsciousness had developed, gradual improvement occurred, and about 15 hours after the oil had been given the animal appeared to return to normal. This improvement generally was temporary; the animal then gradually weakened, and within 36 to 72 hours after administration of the oil coma developed and death followed. Autopsy of these animals consistently showed advanced fatty degeneration of the liver.

Dale [6] and Jurss,[7] with use of myristicin, a constituent of the volatile oil, were able to reproduce in animals symptoms identical to those caused by the administration of nutmeg or the volatile oil of nutmeg. They concluded that myristicin is the toxic factor in nutmeg. Autopsy of their animals showed changes in the liver similar to those described by Wallace.

Chemical Aspects.—Nutmeg is known to contain from 5 to 15% volatile oil, 25 to 40% fixed oil, and 5 to 15% ash. The rest is starch, fiber, and water.[8] Power and Solway,[9] in an analysis of this volatile oil, found that 4% was myristicin. The formula for myristicin is $C_{11}H_{12}O_3$, and it is 5-allyl-1-methoxy-2,3,-methylenedioxybenzene. Further analysis of the volatile oil revealed 80% to be dextrocamphene and dextropinene, with 8% dipentene. Also noted were small amounts of eugenol, iso-eugenol, linalool, borneol, terpineol, geraniol, and safrol. In addition, Power and Solway isolated limited amounts of free myristic acid and traces of esters of this and other fatty acids.

Clinical Aspects.—It is apparent from this case and those previously reported that nutmeg in doses of 5 Gm. or more will produce a characteristic clinical syndrome. From one to seven hours after the ingestion of nutmeg symptoms of a burning midabdominal pain, with or without vomiting, may occur. Restlessness, giddiness, and excitement may be noted. Frequently a fear of impending death is reported, and often there is the complaint of a sensation of a heavy weight on the chest. During the next 10 hours drowsiness progressing to stupor

may develop. However, the patient can be aroused; if this is done, delirium and agitation ensue and the patient sinks again into stupor. Some patients may not manifest the early symptoms of toxicity but may display only the late narcotic effect. As a rule recovery is complete within 24 hours. However, large doses of nutmeg may prolong recovery, and periodic outbursts of excitement with delirium may continue for several days or more.

Significant physical findings may include a decrease in blood pressure, with cyanosis and shock. In addition, there may be rapid respiration, tachycardia, dilatation of the pupils, and decreased or absent peripheral reflexes. Several of the early reports suggest that some patients may exhibit, in addition to the usual symptoms and signs, an acute allergic response to nutmeg. This response is manifested by edema of the eyelids, with marked flushing and itching of the face. There also may be an elevation of temperature. These symptoms of an allergic reaction apparently subside quickly.

Some of the laboratory findings in the case I have reported are not entirely understood. Since previous studies did not contain laboratory reports, the chemical determinations recorded in the present case are difficult to evaluate. In this case acidosis was noted, with depression of the values for serum sodium and serum potassium. The serum chloride content was within the normal range.

On the basis of the experimental work on cats by Wallace, Dale, and Jurss it appeared that fatty degeneration of the liver was the end-result of toxic doses of the volatile oil or its derivative myristicin. However, in the case reported here serial studies of hepatic function as well as biopsy of tissue from the liver revealed no evidence of damage to that structure.

Studies of renal function revealed an initial slight elevation of the nonprotein nitrogen value, as well as albumin content of grade 2+, although the output of urine during the first 24 hours was normal. The value for nonprotein nitrogen returned to normal the next day, and a subsequent urinalysis disclosed occasional traces of albumin. It seems probable that in the case presented here nutmeg produced a transient toxic effect on the kidney.

Summary

The toxic factor of nutmeg is known to be myristicin, a constituent of the volatile oil of nutmeg. Nutmeg in doses of 5 Gm. or more produces a marked depressive action on the central nervous system, as well as a less prominent stimulating effect. The clinical course may be severe, with coma, shock, and acidosis as its main features.

117 W. Boscawen St.

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UNDERNUTRITION AND ENDOCRINE DISTURBANCES.—Most patients with this disease [anorexia nervosa] at one time or another are suspected of primary hypofunction of the pituitary or of the adrenal cortex. . . . It is now becoming well recognized that undernutrition itself may lead to multiple endocrine disturbances. Undernourished subjects may show evidence of underfunction of the pituitary, thyroid, gonads and adrenals; Selye cites undernutrition as cause of adrenal exhaustion in his general adaptation syndrome. The whole relationship of the nutritional status to the endocrine system has recently been reviewed by Kennedy and McCance, who point out that multiple endocrine, as well as psychic, disturbances may be mediated through a final common pathway in the hypothalamus. However that may be, hypofunction of any of the endocrine glands does not readily explain . . . body fluid abnormalities . . . [such as] retention of chloride, sodium and water, depletion of potassium and protein, or redistribution of hydrogen.—J. R. Elkinton and E. J. Huth, Body Fluid Abnormalities in Anorexia Nervosa and Undernutrition, *Metabolism: Clinical and Experimental*, July (Part 1), 1959.

THE PHARMACOLOGY OF MYRISTICIN
A CONTRIBUTION TO THE PSYCHOPHARMACOLOGY OF NUTMEG

EDWARD B. TRUITT, JR., PH.D.; ENOCH CALLAWAY III, M.D.;*
MONIQUE C. BRAUDE, M.S.; AND JOHN C. KRANTZ, JR., PH.D.

ABSTRACT

The pharmacologic and toxic effects of myristicin have been examined in laboratory animals in order to estimate its safety in man. Myristicin is assumed to be the principal active ingredient of nutmeg powder. In 400 mg. doses, myristicin produced mild cerebral stimulation in human subjects. This effect is much less than that produced by 15 gm. of nutmeg powder, which was taken by one of the authors in order to describe its psychopharmacologic action. Removal of the volatile components of nutmeg eliminates the psychic action but not all of the side effects. It appears that myristicin does not reproduce the entire activities of whole nutmeg.

Nutmeg is the seed of *myristica fragrans*. The ground seed has been used as a condiment for centuries. The seed contains a volatile oil to which it owes its fragrance. Different varieties of nutmeg contain from 5 to 15% of the volatile oil. The oil has had limited medicinal use and is believed to elicit properties of a carminative and cerebral stimulant similar to camphor. The volatile oil contains many aromatic constituents; the principal one is myristicin, which is present to the extent of about 4%. The oil contains more than 80% of inert hydrocarbons pinene and dipinene.

Our interest in myristicin stems from the fact that last year three cases of nutmeg intoxication were called to the attention of one of the authors (John C. Krantz, Jr.). Green [1] reported a severe case of nutmeg poisoning in a 28-year-old woman from the ingestion of 18.3 gm. of nutmeg. Excitation of the central nervous system followed by depression and coma was the predominant clinical feature of the intoxication. In the main, in cases of nutmeg intoxication, individuals had ingested one to two ounces of the ground nutmeg, which appeared to produce a prolonged period of delirium, disorientation, and a syndrome comparable to alcoholic inebriety. We have found that this practice is not uncommon among alcoholics who are deprived of the use of alcohol.

Dale [2] published a note on nutmeg poisoning. He states that the active constituent is the volatile oil. Cats were found to be especially sensitive to nutmeg and succumbed to 5 to 10 gm. doses. Fatty degeneration of the liver appeared to be the cause of death. Dale found that in man central nervous system symptoms of narcosis, excitation and delirium prevailed a few hours after ingestion of nutmeg. Power and Solway [3] found the dog insensitive to nutmeg intoxication and confirmed the observations of Dale of the susceptibility of the cat to intoxication by nutmeg; and further stated that nutmeg was frequently used with gin by women in London to produce abortion. Christomanos [4] observed that the feeding of large quantities of myristicin daily to dogs caused increase in fatty deposit in the liver; on iso-

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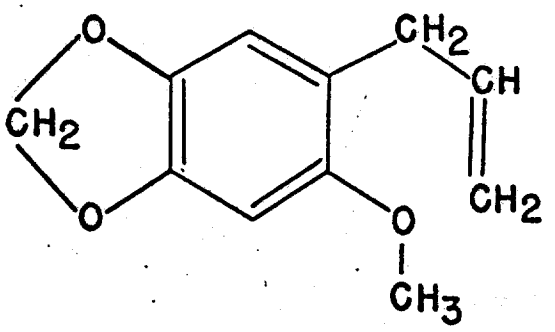
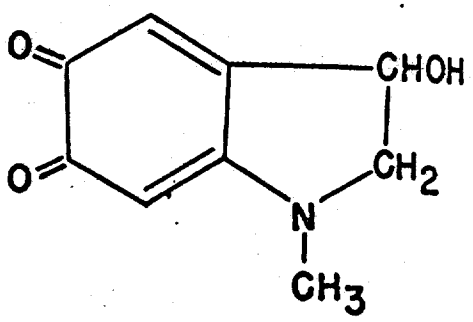
lated smooth muscle strips it was shown to produce a marked decrease in tonus and amplitude of contraction.

Recent interest in reserpine and adrenochrome, each containing an indole nucleus, as competitors to serotonin centered our attention on the active principle of the volatile oil of nutmeg, namely, myristicin. There appears to be a certain spacial structural relationship between adrenochrome and myristicin, as shown by the formulas. (See Figure 1.)



Myristicin



Adrenochrome

Figure 1

A sample of East Indian Nutmeg Oil, U.S.P.,* was fractionated under vacuum. The fraction boiling between 145 and 155° C. at 15 mm. pressure was used for these studies. The recorded boiling point for myristicin is 149.5° C. at 15 mm. This fraction represented 10% of the volatile oil. Refractometer readings indicated a purity of more than 90% of myristicin in the fraction.

In order to determine acute toxicity in rats, a series of 25 white male rats were injected intraperitoneally with myristicin at dosage levels of from 200 to 1000 mg./kg. The estimated LD_{50} appears to be well above 1000 mg./kg. Large doses elicited hyperexcitability followed by central nervous system depression. Owing to the variable data in the literature regarding the toxicity of the two principal varieties of nutmeg, the LD_{50}'s of East Indian and West Indian nutmeg were determined in rats. The LD_{50} of East Indian nutmeg was 0.50 gm./kg. ± 0.14 gm./kg., and that of West Indian nutmeg was 0.70 gm./kg. ± 0.25 gm./kg. Upon steam distillation for the purpose of removing the volatile constituents, the LD_{50} was increased to 1.72 gm./kg. ± 0.59 gm./kg. for East Indian nutmeg and 1.73 gm./kg. ± 0.40 gm./kg. for West Indian nutmeg. These results confirm the fact, as shown in experiments made by Wallace [5] on the cat, that the volatile fraction is largely responsible for the toxicity of whole ground nutmeg.

Twelve young male white rats were placed on a standard laboratory ration. They were given food and water *ad libitum*. A similar group of rats were treated in the same manner but in addition received 10 mg./kg. of myristicin daily in the food. The body weights were determined three times a week for a period of 26 days. The food intake of the experimental animals was approximately 4 kg. during the course of the feeding study. These animals ingested 600 mg. of myristicin. The control group ingested approximately 5 kg. of ration. There was one death in each group. At the end of the experiment, 6 animals in each group were sacrificed for gross examination of the viscera. Nothing abnormal was revealed. Histologic studies of the livers and kidneys showed no abnormalities that could be attributed to the experimental diet. A growth curve of these animals is shown in Figure 2.

An examination of the data indicates that the ingestion of myristicin at this level had no deleterious influence upon the growth of the white rat. Furthermore, the intraperitoneal injection of quantities up to 1500 mg./kg. produced no liver or kidney damage.

It has been well established that reserpine,

* This sample was generously prepared for us through the courtesy of the laboratories of Magnus, Mabee and Reynard, Inc., New York City.

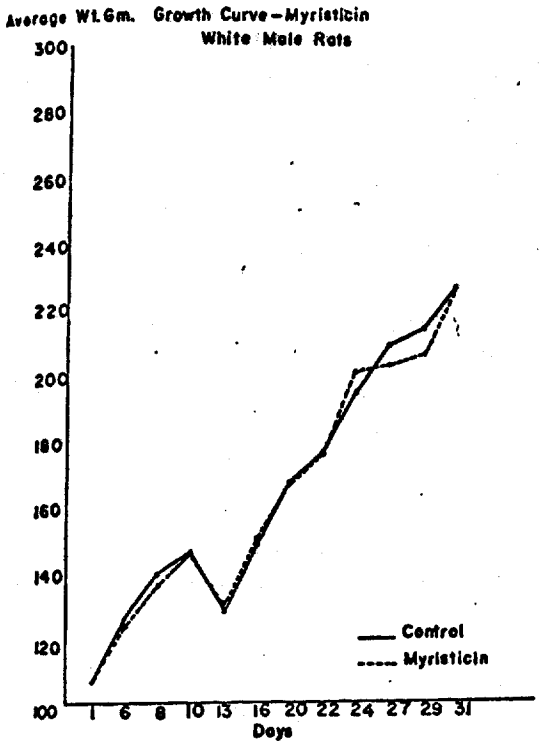


Figure 2

containing an indole nucleus, and chlorpromazine each synergize the action of narcotics and hypnotics. The effect of myristicin on the sleeping time of rats treated with phenobarbital was investigated. The data on 10 rats in each group are shown in Table I.

TABLE I

THE EFFECT OF MYRISTICIN ON THE SLEEPING TIME INDUCED BY PHENOBARBITAL IN THE RAT

Group	Mean Sleeping Time	Standard Error	p Value
Phenobarbital 120 mg./kg. I. P.	162 min.	±5.31	
Phenobarbital 120 mg./kg. I. P. plus 100 mg./kg. myristicin I. P.	144 min.	±2.27	<0.01

It is clear from the data in Table I that myristicin significantly diminishes the sleeping time of rats treated with phenobarbital.

Two mongrel dogs were prepared for blood pressure studies under ether anesthesia. Myristicin was prepared in a 10% suspension in acacia solution. In each instance a fall in blood pressure of about 20 mm. of Hg. occurred upon the injection of 5 cc. intravenously. The duration was about ten minutes.

In order to study the effect in monkeys of repeated intravenous injections of myristicin, it was prepared in suspension by means of polysorbate 80 (Tween 80). Doses of 50 mg. to 75 mg./kg. evoked ataxia and disorientation which lasted for two to three hours. The monkeys lost none of their jungle characteristics. These injections were repeated on five successive days, with the same results. Recovery appeared to be complete. Monkeys injected intravenously with 100 mg./kg. showed respiratory arrest, but were revived by artificial respiration.

In one monkey who was treated with 1 mg./kg. of chlorpromazine one-half hour prior to the injection of 50 mg./kg. of myristicin, the ataxia, disorientation and motor incoordination were masked by the chlorpromazine.

Another monkey was on two occasions given 5 gm. of nutmeg in acacia suspension by stomach tube. Observations over a 24-hour period showed no changes in behavior characteristics. Visual acuity, reflex time and other activities of the animal appeared to be unaltered by the drug.

A cat was given 2 mg./kg. of morphine sulfate intraperitoneally. A typical sham rage and ataxia occurred. Thirty-five minutes later 50 mg./kg. of myristicin was injected intraperitoneally. The syndrome was aggravated by the myristicin. Within a few hours the animal became depressed and catatonic and failed to respond to external stimuli. Respiration was slowed and the animal was found dead the next morning. It does appear that cats are especially susceptible to the action of myristicin.

For the initial evaluation of myristicin in humans, we selected as a subject a jazz musician who had experienced the effects of many intoxicating drugs. He was started at a dose of 25 mg. orally and this dose was doubled weekly until a dose of 400 mg. was achieved. At no time did the subject experience any symptoms.

In order to study the effects of myristicin in 10 subjects, the investigator was furnished with two sets of identical capsules; capsule A containing a bland oil and a placebo, and capsule B containing 400 mg. of myristicin.

Ten "normal" control subjects were given the pair of capsules with instructions to take one on one day and one on another. They were asked to pick days that were as alike as possible and were told to take each capsule at approximately the same time of day. Finally, the subjects were asked to record their reactions to each capsule. Neither the investigator administering the capsules nor the subjects knew which contained the active compound and which contained the bland oil.

The majority of the subjects were unaware of any of the alleged effects of myristicin and did not know what to expect from the compound. The experimental population consisted of 4 physicians, 2 medical students, a technician, a secretary, a biochemist and a psychologist. Two of the subjects were women and 8 were men. The results may be summarized as follows:

No noticeable reaction to either capsule—3 subjects.
Questionable reaction to capsule A—1 subject.
Questionable reaction to capsule B—2 subjects.
Definite reaction to capsule B—4 subjects. (Of these, 2 had a pleasurable and 2 an unpleasant reaction.)

Details of reactions to the capsules are listed below:

Questionable reaction to capsule A(placebo):

The subject stated that after capsule A he felt more euphoric.
Things were going well on that day, however, and he felt that this might simply be the reaction to environmental success.

Questionable reactions to capsule B:

(1) Some hours after taking the capsule this subject began to notice gastrointestinal symptoms. This subject's family was suffering from a grippal condition at about the same time and were experiencing similar symptomatology. The subject ended his description of his symptoms as follows: "Since my wife and kids also have them (symptoms) I think it is infectious. There were no effects which I could relate distinctly to the drug."
(2) Subject stated that she took capsule B at 11:30 a.m. At 4:30 p.m. she suddenly felt extremely tired and depressed and on arrival home she had an altercation with her fiance. She was not sure that this was due to the medication since it had been a rather strenuous day.

Definite pleasant reactions to capsule B:

(1) About 2 hours after taking the drug, this subject noticed a mild feeling of increased alertness. The subject was more free in making comments at a staff conference than usual and in general felt more wide awake during the morning and immediately after lunch than is usual. There was a slight feeling of restlessness but no tachycardia. At one point there was a rather unusual feeling of tingling and numbness about the face and the mouth; this was rather mild and lasted only a few moments. Sixteen hours after taking the drug, the subject suffered an attack of diarrhea.
(2) The subject took her capsule at 7:30 a.m. At 8:45 during a psychoanalytic hour there was flushing, sweating, a sense of lightheadedness and a feeling of being detached. The subject felt that she talked more freely and had less of a tendency to weigh and measure her words. She experienced a mild perceptual distortion and a general feeling that the physical surroundings were somewhat fluid. Distances seemed variable. On leaving the analytic hour there was a sense of detachment which the subject felt led to reckless driving and a feeling that nothing would happen. Throughout the day the subject experienced periodic flushing and a feeling of euphoria. The subject was talkative, laughed a great deal and felt rather insensitive about what others might think or say. There was some difficulty in concentrating and a general feeling of restlessness.

Definite unpleasant reactions to capsule B:

(1) The subject stated that about an hour after taking capsule B he began to be nervous. He experienced a slight tremor and

effective work around the house. I was quite content to lie still and look at nothing. By Friday evening at supper time I was feeling a good deal better. I had a drink before dinner and went to bed promptly after dinner and slept through the evening again. By Saturday morning I was feeling quite well and was able to drive the car again, although some vague feelings of detachment and unreality were detectable from time to time."

In summary, 15 grams of nutmeg produced a reaction, starting about an hour or two hours after ingestion, and reaching a peak that ranged from about six hours to about 24 hours. The effect did not disappear until approximately 36 hours after ingestion. The symptoms were marked by vaso-motor instability, tachycardia, hypothermia, absolute absence of saliva, constricted pupils, some emotional lability and a tremendous feeling of isolation and inability to carry on intellectual processes.

Since the quantity of myristicin ingested by the previous subjects did not reproduce the character or intensity of response elicited by ground nutmeg, the question arose as to whether or not the response is dependent upon myristicin. Accordingly, two of us (Monique C. Braude and Edward B. Truitt, Jr.) ingested 10 grams of nutmeg which had been previously deprived of all its volatile constituents. The characteristic psychopharmacologic effects of whole ground nutmeg were eliminated but some undesirable side effects remained. These consisted of occasional flushing, lower intestinal discomfort and unusually heavy sleep in one case (M.C.B.); and lower intestinal discomfort and insomnia in the other case (E.B.T.). This suggests that the other volatile constituents (safrol, borneol, linaloöl, eugenol, isoeugenol and geraniol) in nutmeg contribute markedly to its psychopharmacologic effect in man.

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Accidental Chemical Poisonings

From the Poison Control Center
The City of New York Department of Health

A series prepared by

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Medical Director, Poison Control Center
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Poison Control Center

Poisonings Due to Mace (Nutmeg), Furniture Polish, and Lead

THE FOLLOWING INCIDENTS have been reported to the City of New York Department of Health Poison Control Center.

Mace (nutmeg) intoxication

On November 4, 1963, an inquiry was made to the Poison Control Center on the management of mace (nutmeg) intoxication which was reported by Jacob Horowitz, M.D., the Medical Director of the Department of Correction, of which Rikers Island, a penal institution for adolescent inmates, is a part.

CASE 1. The victim was an eighteen-year-old male inmate who had a previous history of drug abuse since the age of fifteen years. He reportedly used heroin and barbiturates. The patient acquired the habit during a confinement at Riverside Hospital, a facility for the treatment of juvenile narcotic addicts. He initially obtained the drug at Riverside from another inmate who also taught him how to mix the spice with water. The patient also related to the attending physician that the effect produced by this concoction was similar to the effect which he obtained from taking marijuana. According to the reporting physician the patient gave the following story:

On October 26, 1963, he obtained a half can of mace from another inmate who was being discharged. The can was a standard size, by 2.5 by 1 inches. He made a solution of the spice and drank it all at 5:30 A.M. At 10:00 A.M. he felt hot, dizzy, and weak. He was taken to the Rikers Island infirmary and was seen by the physician. The boy was in shock at the time but responded readily. The physician called the Poison Control Center for advice. After he returned to normalcy the patient complained of a heavy feeling in his abdomen. He was rational and answered whatever questions were put to him by the physician. The patient apparently made a complete and rapid recovery.

COMMENT. Mace contains a mixture of essential oils. Nutmeg contains from 7 to 16 per cent of oxygenated volatile oil and about 35 per cent of fatty oil. This product is widely used in the flavoring of foods because of its stimulating aromatic and carminative effects. The adult dose is 0.5 Gm., and the ingestion of 4 to 5 Gm. of nutmeg has been reported to be toxic. The toxicity is reportedly due to the presence of myristicin ($C_{11}H_{12}O_3$). The combination of volatile oils of nutmeg and mace is practically identical. Nutmeg oil is derived from the dry kernel of the seed and mace from the dried exterior coating of the brown shell which contains the seed. Nutmeg is particularly dangerous because of its action on the central nervous system.

The following symptoms have been reported from the ingestion of 1 to 5 nuts

headache, dizziness, flushing of face and sometimes swelling of face and eyelids, numbness of limbs, thirst, disorientation, stupor, abdominal pains, vomiting, oliguria, cold perspiration, and clammy skin. It may also be mentioned that nutmeg is being used as an abortifacient but is of doubtful efficacy. Symptoms may be delayed and will appear from one to six hours later.

In the *New England Journal of Medicine* Payne* describes 2 cases of nutmeg intoxication in 2 male college students nineteen and twenty years of age respectively. They invested 2 tablespoonfuls (14 Gm.) of a commercially available powdered nutmeg suspended in a glass of milk which was recommended to them in the belief that it will provide a mental state similar to ethanol intoxication without the use of alcohol. About five hours following the swallowing of this concoction the students experienced an unreal or dreamlike mental state. About twelve hours following ingestion they had extreme drowsiness which lasted for about twenty-four hours, and the state of unreality in these cases lasted for about sixty hours. In both cases recovery was uneventful.

The common denominator in most of the reported cases of nutmeg poisoning is the exhilarating effect such as excitation on the central nervous system. While the symptoms and euphoria may be bizarre and alarming, an uneventful recovery usually follows and fatalities are rare. There is no specific antidote for nutmeg intoxication, and the treatment is in the main supportive and symptomatic including gastric lavage.

Inmates of hospitals of penal, corrective, and mental institutions and also military personnel have been found to be indefatigably ingenious in diversion of products found in institution pharmacies, paint shops, hobby classes, garages, mortuaries, and so forth, in attempts to obtain real or fancied stimulatory effects from their inhalation, eating, or injection. The kitchens of such institutions should be added to the areas which must be carefully screened and constant vigilance maintained. In addition to nutmeg we have had reports from institutions involving vanilla extract "wood" alcohol, and solvents. The central nervous system effects observed by inmates exposed to solvents may have been influenced by poor ventilation of working conditions in these institutions. Carbon tetrachloride and benzene should be excluded from any list of solvents used in such places. The labeling problem in institutions is aggravated by the fact that the Federal Hazardous Substance Act does not apply to large containers (not in New York State). The staff of such institutions have a special responsibility to supervise proper labeling, to discourage dangerous diversion, and provide intelligent warnings.

Narcotic and alcohol users, particularly adolescent beatniks, not infrequently resort to exotic products including nutmeg to obtain an exhilarating effect which they presumably obtain from drugs or alcohol when the latter becomes unavailable to them.

The medical director of the Department of Correction submitted a list of all condiments and spices used by that institution for an opinion as to whether any of these would present any similar problem. They were found to be of a nontoxic variety.

Furniture polish: a petroleum distillate

CASE 2. The mother of the victim was polishing furniture with a widely used household furniture polish. The telephone rang and the mother left to answer the phone, and in the interim the one-year-old infant obtained the bottle which the mother left on a low table and swallowed an unknown amount of its contents. When the mother returned from the telephone call she noticed that the child was in a stupor, and she then remembered the furniture polish which was left within the child's reach. According to the mother the child merely tasted the product and did not swallow any appreciable amount. The child was taken to a nearby hospital emergency room where the stomach was lavaged with milk presumably about one hour after ingestion.

On admission to the hospital the child was dyspneic and cyanotic, with tonic convulsions and coma. The chest x-ray film showed a bilateral bronchopneumonia. In spite of emergency and supportive therapy the patient expired about four and a half hours after admission to the hospital and

* Payne, R. B.: Nutmeg intoxication, New England J. Med. 269: 36 (July 4) 1963.

about six hours following ingestion.

The admission diagnosis was petroleum naphtha poisoning accompanied by bronchopneumonia. A pertinent portion of an autopsy report which was obtained through the courtesy of Milton Helpern, M.D., Chief Medical Examiner, follows:

> External description: Body is that of a Negro, female infant child, showing dark brown hair, brown eyebrows, and brown irides.
>
> Head: Brain weighs 1,050 Gm. There is moderate congestion and edema of the brain.
>
> Chest: Interthoracic organs in usual site and location; compatible size for age.
>
> Respiratory system: Lungs are almost completely consolidated, except for a small area around the fringe. Cut sections sink in water.
>
> Cardiovascular system: Heart is grossly normal.
>
> Hepatobiliary system: Liver weighs 330 Gm. Cut section is normal.
>
> Gastrointestinal system: Stomach contains slight amount of curdled milk and gray-tan mucus. There are no gross ulcerations noted.
>
> Pancreas: Pancreas is normal in size and appearance.
>
> Spleen: Spleen is 30 Gm., is dark red-purple in color.
>
> Genitourinary system: Normal genitourinary system. Bladder is distended, with 4 ounces of straw-colored urine. Genitalia are normal.
>
> Anatomic findings: (1) bronchopneumonia, (2) visceral congestion, and (3) cerebral edema.
>
> Cause of death: Bronchopneumonia secondary to petroleum poisoning.

COMMENT. It is to be noted that stomach lavage was used in this case as a therapeutic measure. This is a procedure which is not considered to be a treatment of choice. As a matter of fact we have repeatedly advised against the use of gastric lavage in petroleum distillate poisonings. The rapidity with which death ensued in this case is noteworthy since in the majority of cases of petroleum distillate poisonings one encounters a delay in manifestations of symptoms and particularly severe complications. The majority of our cases of petroleum distillate swallowing by children are not accompanied by serious sequellae.

We take advantage, however, of this opportunity to remind physicians again that although children who swallow petroleum distillate may not present any symptoms, they should definitely be hospitalized for a period of from twenty-four to thirty-six hours, and serial x-ray films should be taken during their stay to insure that a pneumonitis is not present and that the child is promptly and appropriately treated.

There are several insidious factors to the problem of petroleum distillate poisoning. One is the various guises in which they occur in the home and which may not be recognized at the moment by the physician, such as insecticides, barbecue lighter fluids, cigaret lighter fluids, some anti-rust preparations, some cosmetics, polishes, paint products, spot removers, and varnishes. Because of the universal use of petroleum products in the home and the lack of hazard to the adult user, the warnings appearing on these products, such as "may be fatal," "dangerous to children," become blunted. The average mother would not think of leaving an unattended young child within easy reach of a dangerous drug to answer a telephone, as happened in this case.

At the present time two important facts emerge from this situation. One is to revise the warnings on these products so that they will not be regarded as ordinary household agents. There is apparently a dire need for a better labeling message on these packages. Second, at the physician's level to warn mothers repetitiously about these apparently "harmless" household products. It is difficult to overcome generations of carelessness in the use of furniture polishes. The severity of these poisonings merits that they should be treated as are potent drugs in the household environment.

The hazards associated with petroleum products have only been publicized in recent years. One wonders therefore about the true magnitude of the problem and the suspected large number of unreported cases in the past.

Lead poisoning

CASE 3. A girl, age five years, was admitted to the hospital with generalized convulsions. The mother related that she was unaware of the child's eating lead paint-containing substances. A history of pica, however, was obtained, but the mother stated she did not know that this practice was harmful. On further questioning the mother related that for two months prior to admission the child had complained of generalized pain in the abdomen and that she had taken the child on several occasions

to an outpatient department clinic, but on examining the child some medication was prescribed and the child was sent home.

On the final admission to the hospital the patient was convulsing and comatose. The lead blood level was 0.05 per 100 ml. of blood. The urine was strongly positive for acetone, and the cerebral spinal fluid protein was elevated. The flat abdominal plate revealed radiopaque particles in the large and small intestines. Lead lines were observed in the long bones. Before any therapeutic measures could be instituted the patient expired, approximately six hours following admission.

Microscopic examination revealed the following:

Lungs: The lungs show abundant precipitated acidophilic edema fluid and slight hemorrhage into alveoli. One section shows more extensive hemorrhage and focal atelectasis. Some bronchioles show neutrophils and lymphocytes in their walls.

Trachea: The trachea shows congestion and intense plasma cell infiltration of the submucosa.

Spleen: The red pulp is congested and shows neutrophilic infiltration.

Liver: The liver appears normal.

Pancreas: The pancreas is unremarkable.

Intestine: The esophagus shows mucosal ulcerations and infiltration by neutrophils and macrophages.

Ileum: The ileum is unremarkable.

Appendix: The appendix shows abundant submucosal lymphoid tissue.

Adrenals: The adrenals show the usual postnasal involution.

Kidneys: The convoluted tubules throughout the cortex of the kidneys show considerable variation in appearance of the nuclei of their lining epithelial cells. Some are shrunken and palish-stained, and others are markedly enlarged and hyperchromic; still others exhibit presence of acidophilic intranuclear inclusion bodies. Other tubules show proliferation of cells lining tubules. There is considerable patchy congestion of cortex and medulla.

Ovaries: The ovaries show numerous primordial ova and maturing follicular cysts.

Thyroid: The thyroid is unremarkable.

Thymus: The thymus shows congestion.

Lymph nodes: The lymph nodes show marked hyperplasia of lymphoid tissue and patchy congestion.

Brain: Multiple superficial changes of the brain consist of elevation of pia mater with subpial accumulations of vacuolated, mononuclear cells. Elsewhere, there are multiple areas of vacuolation of white matter. Some ganglion cells show nonspecific degenerative changes.

Bone: The spicules are thick. The marrow shows erythroblastic hyperplasia. No osseous architectural changes are noted.

The general and anatomic diagnosis was as follows: (1) lead poisoning; (2) edema and recent hemorrhages of lung; (3) chronic bronchiolitis and tracheitis; (4) acute ulcerative esophagitis; (5) recent gastrointestinal hemorrhage; (6) hyperemia of jejunal mucosa; (7) hyperplasia of lymphoid tissue of mesenteric nodes; (8) nuclear atypia with intranuclear inclusions of renal tubular epithelium; (9) congestion of kidneys, spleen, and liver; (10) erythroblastic hyperplasia of bone marrow; and (11) focal degenerative changes (microscopic) of central nervous system.

It is significant that the lead blood level on admission which was only six hours prior to death did not exceed 0.05 ml. per 100 ml. of blood. Such observations have been noted in previous cases and in several cases of lead intoxication associated with lead encephalopathy. This would indicate that acute lead intoxication cannot be ruled out merely because the blood lead level is below 0.06. The significance of this apparently low blood lead level is puzzling. The child's age is also in the upper limit. Usually the fatalities occur in children below four years of age.

The public health nurse who visited the home reported that the conditions in the home were bad including cracks in the walls and loose painted plaster on the floors in the bathroom and halls.

CASE 4. A four-year-old child was admitted to New York Hospital and according to the report received from the hospital the following history was obtained.

The patient was entirely well until June, 1963, when she was noted to toe in on the left. She was examined at a child health station and referred to the New York Hospital. The patient showed marked behavioral changes such as doing apelike movements of both arms when there were visitors in the home, marked unresponsiveness to commands, marked hypoactivity, insisting that an individual was hiding in the room and that a cat was in the room chasing her, and lying to the mother about eating food and hiding it in unusual places. All these are marked personality changes from previous behavior.

She was seen at the Hospital for Special Surgery for a left toe-in, was advised to wear a pediatric shoe, and was referred to the pediatric outpatient department. The ex-

amination revealed a markedly quiet child with a left toe-in. Her hemoglobin was 11.8 Gm., hematocrit 35.5, eosinophils 2 per cent, no basophilic stippling; the electroencephalogram was normal, there was a negative twenty-four-hour urine for coproporphyrins, but a serum lead level of 0.07 mg. per 100 ml. was obtained. The elevated serum lead level suggested a lead encephalopathy as a possible etiologic basis of the child's behavior and abnormal gait. The patient's home was visited by the health department sanitarian and a search made for a source of possible lead intoxication, but this was said to have been negative since the home, while not new, was not an old one and had not been painted with known lead paint. The child had a questionable history for pica and was admitted to the inpatient service for evaluation of a possible lead encephalopathy.

The family history was noncontributory except that the patient was born in Buenos Aires, Argentina. At the age of two months the patient's family moved to Chile and remained there for two years until the occurrence of severe earthquakes when the family came to the United States. It is reported that because of the earthquakes the mother was extremely nervous and the child likewise became highly sensitive.

Past history: Three weeks prior to the present admission the child suffered from a conjunctivitis of the right eye, poor appetite, and frequent constipation.

Physical examination: Temperature 37.6 C., pulse 120, blood pressure 110/60, respiration 20. A quiet, cooperative, well-nourished, well-developed female in no acute distress. Extremities showed pronounced tibial torsion on the left, some suggestion of equinus on the left. Neurologic findings were a questionable decrease in strength of the left leg and left arm. The gait was wide, broad-based, with a left foot drop and toe-in; arms were held in an outward rotation and apelike fashion.

Laboratory: The blood showed a hematocrit of 38; white blood cells 7,800, with 50 per cent lymphocytes, 3 per cent monocytes, 44 per cent mature polymorphonuclear leukocytes, and 3 per cent bands. No basophilic stippling of erythrocytes. Urine showed a specific gravity of 1.027, pH 5.5, negative protein and sugar, and negative microscopic findings. Nose culture showed Staphylococcus aureus heavy. Throat culture showed Staph. albus and gamma streptococcus. The blood culture and tuberculin test (PPD) were negative.

Course: Following admission a lumbar puncture was done which was entirely within normal limits except for an opening pressure of 225, closing pressure 140 with the patient at rest. Repeat lumbar puncture ten days later was entirely within normal limits with an opening pressure of 140 and a closing pressure of 90. Work-up for lead toxicity revealed a repeat serum lead level of 0.06 mg. per 100 ml. Urine lead level and urine coproporphyrins before and after edetate calcium-disodium (Versenate) were all entirely within normal limits. Abdominal and long-bone x-ray films showed no evidence of lead or lead lines. Orthopedic, neurologic, and neurosurgical work-ups were entirely unrevealing as to the possible etiologic source of the abnormal gait. Skull x-ray films gave normal findings. The patient was observed on the ward and in the playroom, particularly while she was unaware of being observed, and was noted to have an almost normal gait on a number of occasions. She was seen by a psychiatric consultant, and it was felt that the patient might well benefit from further psychiatric evaluation and work-up should any organic cause for her abnormality be found. She was discharged to be followed in the pediatric clinic with possible referral to the psychiatric clinic.

The public health nurse who visited the home obtained a history that the child had been eating paint off her toys since infancy, and the mother denied that the child had ingested any painted plaster or had chewed on other painted surfaces. This finding is in variance with our New York City experience where we have as yet been unable to document any confirmed case of lead poisoning due to the ingestion of painted toys. It would appear, however, that Chilean toys are incriminating. The nurse also related that the family owns their own home which is comfortably furnished and well maintained. The child was referred to the child health station for further follow-up.

While the abnormal manifestations including the abnormal gait are not characteristic of lead poisoning, the history during infancy about the child's sensitivity following the earthquakes coupled with lead poisoning may explain the bizarre behavior. Thus this case may be a combination of lead encephalopathy causing or concurrent with the emotional disturbance.

CASE 5. This two-year-old white female child was admitted to the hospital on three successive occasions within four months. There was a history of pica associated with lead poisoning. The child was admitted each time in a comatose condition with diarrhea and convulsions and treated with

edetate calcium-disodium with temporary improvement. The family appeared indifferent and the public health nurse who visited the home remarked that the mother could have been more alert and attentive to the child's needs but that she did not seem fully aware of the existing hazard.

On the final admission the child was admitted to the hospital with a diagnosis of lead poisoning and lead encephalopathy. Following treatment and improvement, the child was discharged with instructions for a home nursing care program. However, approximately ten days following discharge, the child was returned to the hospital in coma. Following admission, the comatose condition deepened, and the child had numerous convulsive seizures. The child was unresponsive to therapy and expired on the third hospital day.

The following is the postmortem report:

The body is that of a normally developed, somewhat undernourished female child, approximately two years of age. The head has a diffuse growth of long black hair. The eyes, ears, nose, and mouth are unremarkable. There are no unusual masses in the neck. The thorax is symmetrical. The abdomen is flat, and no abnormal masses are felt. There is no abnormal lymphadenopathy. The extremities are normal except for several needle punctures on the left buttock. The external genitalia are normal. Over the skin of the abdomen there is a somewhat more than usual growth of fine black hair. Rigor is prominent in the extremities, and there is considerable livor over the dependent portions of the body.

The esophagus, stomach, and intestines are essentially normal. There is a small amount of coffee-ground material in the stomach and upper intestinal tract. Throughout the mesentery of the small bowel there are numerous enlarged lymph nodes. The liver is somewhat congested and weighs 350 Gm. The spleen weighs 30 Gm. The pancreas has a normal architecture. The kidneys weigh 75 Gm. Except for distention of the urinary bladder with clear amber urine, the urinary tract is not remarkable.

The cranial cavity appears to contain some excess of cerebrospinal fluid, and the surface of the brain appears to be edematous. After removal of the brain, a hemorrhagic area was noted on the undersurface of the left temporal lobe, and there is in this area a small rent on the surface of the brain through which clotted blood may be seen within the substance of the brain. A small incision in this area reveals a massive hemorrhage occupying much of the temporal lobe. Further examination of the brain is postponed for further fixation.

Microscopic: The brain has extensive areas of necrosis and hemorrhage. Several of the smaller cerebral vessels are thrombosed, and a few vessels have perivascular hemorrhage. Other organs have extensive congestion. Within the adrenal glands there are a few small vessels that appear to be occluded by thrombi, but no associated infarction is seen. The mesenteric lymph nodes have a nonspecific lymphadenitis. The endocardium of the left atrium is thickened.

COMMENT. One wonders, of course, whether a child who is so severely ill and brought to the hospital at such frequent intervals with a preventable illness should be returned into the same hazardous environment. It would appear more appropriate in dealing with a family which exhibits indifference and where frequent admissions for lead poisoning are encountered to refer such children to social service for possible temporary placement in a more suitable environment.

In the course of the last few years we have had a number of visitors from England who have repeatedly insisted that lead poisoning does not occur in England. We suggested that the absence of lead poisoning in England may be due to a lack of a low index of suspicion about the existence of lead poisoning and as a matter of fact we have suggested to some of our visitors that on their return they make an intensive search for such cases. One visitor eight months following his visit reported that he had already found more than a score of cases of confirmed lead poisoning. It is a matter of little satisfaction that there had been a recent surge of clinical reports in the British literature about the occurrence of lead poisoning in children and the acceptance of the fact that the majority of the cases occur in houses of Victorian vintage which were painted when high lead-containing paints were in vogue.

CASE 6. A report received from the Jewish Hospital of Brooklyn indicates that this boy was admitted to the outpatient department at the age three and a half years for a routine check-up. It was noted, at that time, that the child did not speak at all and that he was apparently mentally retarded. A tentative diagnosis of lead encephalopathy was made, and he was referred to the neuromuscular clinic for further work-up. The diagnosis of lead encephalopathy was based on the fact that the child would eat paint, dirt, and anything else he could loosen with

his nails. It was noticed that he was extremely hyperactive, with exaggerated knee jerks, and that his loss of speech was rather recent. The child previously had a vocabulary of about 25 words.

An electroencephalogram was within normal limits. X-ray films of the skull showed negative results. A supine film of the abdomen revealed the bony structures to be intact. The visceral and psoas shadows were not remarkable. The gas distribution was within normal limits. Opaque material was found to be scattered throughout the colon. A repeat film of the abdomen taken a month later still showed opaque material in the intestinal tract. A repeat film taken three months later showed no evidence of radiopaque material in the abdomen. The blood lead level was 0.36 mg. per 100 ml. (normal level is 0.04). A twenty-four-hour urine specimen was negative for coproporphyrin, uroporphyrin, and protoporphyrin. Complete blood count revealed a hemocrit of 36, a hemoglobin of 12.5 Gm., and a normal white blood count. A second blood level for lead revealed a level of 0.6 with positive uroporphyrin in the urine. He was therefore admitted to the hospital in an effort to delead him, the diagnosis being chronic lead poisoning with secondary encephalitis and mental retardation because of brain damage.

A second electroencephalogram done six weeks after the first showed more slowing in low-voltage activity in all leads. The pattern was irregular from mixed frequencies. The impression was that the electroencephalogram was abnormal for the patient's age with a hint of focus on the right at the temporal areas.

The child was placed on edetate calcium-disodium 600 mg. twice a day, and was discharged to the outpatient department.

After he was followed for three weeks in the outpatient department, the blood lead level showed a slight drop from 60 mg. per 100 ml. It was therefore decided to readmit the patient for another course of edetate calcium-disodium therapy. After this second course of treatment the patient was again discharged to the outpatient department for follow-up, but when last seen about a month later his blood lead level again rose to 60 mg. per 100 ml. and the patient was again admitted to the inpatient services for further deleading.

It is interesting that this patient was also seen at another hospital nine months prior to his first admission to Jewish Hospital of Brooklyn and at that time the patient's clinical record did not mention lead poisoning.

CASE 7. A twenty-three-month-old girl was admitted with a history of vomiting with progressive weakness for four days. The patient was previously seen by a private physician who gave her some medication and told the parents she had a virus infection. Since then the child had not been taking anything by mouth. A few hours before admission the baby developed twiching of the face, turned cold, and was semiconscious, and so the parents rushed the child to the hospital.

Past history: There was no history of previous illness.

Physical examination: Physical examination showed abnormal findings; the child was under-nourished and moderately dehydrated; temperature 100 F; pupils reacted sluggishly to light; throat congested; breath sounds slightly diminished; no rales appreciated; and the baby was still convulsing (bleeding from the mouth), vomiting coffee-ground material.

X-ray reports: In the long bones there was increased density in the metaphysial regions of the distal tibia and fibula, both sides. There was also increased density in the distal metaphysial region of the metacarpals. There was also increased density in the metaphysial region of both tibia and fibula. The composite findings were of heavy metal ingestion.

Chest: There were no abnormal findings on physical examination.

Abdomen: There was a moderate distention of small and large bowels.

Laboratory findings: The white blood count was 22,850, segments 82, band forms 1, lymphocytes 13, monocytes 4, hemoglobin 9.1, hematocrit 34, nucleated red blood count 10, and no sickle cells. Anisocytosis, hypochromia, and basophilia were present. The chlorides were 115 mg. per 100 ml., carbon dioxide 62 volumes per cent, sodium 137 mEq. per liter, potassium 5.6 mEq. per liter, calcium 11 mg. per 100 ml., and blood lead results 0.09 mg. per 100 ml.

Diagnosis: Chronic lead poisoning with lead encephalopathy.

The patient was put on edetate calcium-disodium therapy 250 mg. daily. In spite of therapy the patient died four days following admission.

When the Department of Health epidemiologist interviewed the mother, a history of pica of six months duration was ob-

tained. The positive findings in this case were gastrointestinal symptoms, a lead blood level of 0.09 mg. per 100 ml., and condensation at epiphysis on x-ray of the long bones.

On the postmortem the positive findings were cerebral edema and congestion of viscera.

CASE 8. A query was received from a zoo about a possible lead poisoning of two monkeys (Gibbons), one of which had died. No blood had been taken for chemical examination, but the police laboratory reported negative results on some of the organs. It was suggested that scrapings from the bars of the monkey cages might be helpful in determining the cause of death.

Chemical examination in the food and drug laboratory of the Department of Health indicated a 10 per cent lead content. This indicates that pica just as in human beings is also a problem in the monkey. It is thus important to be just as meticulous in the selection of paint used for monkey cages as for the crib and home environment of a baby. It is not uncommon to prime outdoor iron works with red lead before painting. Some other nontoxic priming agent is indicated for the maintenance of zoo properties.

COMMENT. It is very gratifying to report that in the last few years very few cases of lead encephalopathy have been reported in New York City. We believe this results primarily from the intensive educational program about lead poisoning carried on by the Department of Health and the ready availability of lead blood determinations which the Department of Health provides free of charge through its laboratories to all physicians and hospitals which request it.

In the past decade the case fatality rate was reduced from 48 to 1.3 per cent, which means that lead poisoning cases are now identified in their incipiency in the asymptomatic stage before brain damage occurs. It is at this time that lead poisoning is more amenable to treatment and may not cause any residual damage.

The following figures are worth stating. In 1953 only 27 cases were reported, 13 of which terminated fatally. In 1964, 509 cases were reported with only 8 terminating fatally. This however does not leave any room for complacency. Our vigilance must be continued since even one fatal case is one too many, and we should not be comfortable until lead poisoning is entirely eliminated from New York City. All housing antedating the introduction of the nonlead-containing paint continues to be a great hazard to young occupants six years of age and under.

The occurrence of more than one case of lead poisoning in a family is not unusual and has been reported with increasing frequency in the past several years. A number of such incidents have been reported to the New York City Poison Control Center. For the past months, however, we have had several cases of triple lead poisonings reported in families and a family in which 4 children were involved.

CASE 9. Family "A" included 3 children ages two and a half and four and a half years and one fifteen months. They were nonwhite living in the Bushwick district of Brooklyn in substandard housing. The 3 children were taken to Kings County Hospital for an investigation relating to tuberculosis contact, and on a routine blood work-up a suspicion of lead poisoning was entertained because the blood lead level on the 3 children was above 0.06 mg. per 100 ml. It may be mentioned parenthetically that this hospital (Kings County) has a very favorable high index of suspicion for lead poisoning and the interns, residents, and attending staff are well sensitized to this disease and employ screening and diagnostic measures which may profitably be emulated by other hospitals. All 3 children were treated for lead poisoning with edetate calcium-disodium.

On admission to the hospital the children did not manifest any overt symptoms. The public health nurse visited the home and alerted the family about the harmful effects of chewing on painted plaster, peelings from ceilings, or gnawing on window sills. The family was very cooperative and concerned and will be periodically followed up by the public health nurse. All children appear well at present.

CASE 10. Family "B" also included 3 children ages one, three, and six years. The first 2 were female and the third was male. This case first came to the attention of the health department when a public

health nurse from the department made a home visit for special investigation for a housing priority requested by the father. A public health sanitarian also went into the home on three different occasions and noted the following: "The conditions found were deplorable. This is a 3-story multiple dwelling, but only this family lives there now. Paint is peeling throughout, there are holes in the walls; there is no railing on the stoop; the brick work on the stoop is defective; and no heat is provided. There are several social problems connected with this family. The mother died of cancer in March, leaving six children, who are now ten, nine, eight, six, three, and one years of age. A girl under eighteen years of age acts as baby sitter during the day while the father is away at work."

During the interview the astute public health nurse discovered that the one-year-old had been chewing painted plaster from the walls. The baby sitter stated that she did not know how long the children had been eating plaster since she had been caring for these children for only a short time since the death of their mother. The nurse then referred all 3 children for lead blood determinations. The lead blood levels were 0.06, 0.07, and 0.09 respectively. All the children were asymptomatic, but a history of pica was obtained on the one-year-old but not on the other 2, perhaps because the person who was interviewed had known the children only for a short period of time. All 3 children were described by the public health nurse who visited the home as of average intelligence, active, and curious. The father appeared very interested, and the children were referred to a nearby child health station for needed child health supervision. Every effort is being made to get this family relocated from this hazardous environment to a "lead-free" apartment. The children were treated for lead poisoning and made an uneventful recovery.

CASE 11. Family "C" was of Puerto Rican origin and included a year and a half male, a two and a half year female, a five-year female, and a three and a half year male. The family was aware that the children were eating painted plaster and peelings from the ceiling. The youngest child in addition to a history of pica on admission to the hospital had anorexia, vomiting, pallor, lethargy, and convulsions. The laboratory findings were hemoglobin 7.2 Gm. per 100 ml. and the white blood cells 13,600; basophilic stippling was also present. The urine contained traces of albumin, 4 plus acetone, and 3 plus sugar. The blood lead level was 0.35 mg. per 100 ml., a very high level. This child was treated with three courses of edetate calcium-disodium intramuscularly; however, after three weeks of hospitalization, this patient recovered. The other 3 siblings had 0.12, 0.08, and 0.07 lead levels, did not have lead encephalopathy, but were diagnosed as having lead poisoning because of a history of pica and a high lead blood level.

The public health nurse visited the home and alerted the parents on the harmful effects of pica and on the need for periodic health supervision. The nurse observed that there was loose plaster on the walls in the bathroom and in the two front bedrooms. An attempt has been made to cover up the gnawed areas. Paint samples taken from the walls of two rooms showed a 12 per cent lead level. On a follow-up visit several months after the initial visit it was found that the rooms were repainted with a lead-free paint.

COMMENT. The familial cases cited are highlighted to show that such occurrences are not limited to communicable diseases but will and do occur in illnesses of environmental origin. Familial or multiple cases result from simultaneous exposure to the same environment and because younger siblings attempt to emulate older siblings.

Whenever a lead poisoning case is found in a family where there are other children under six years of age, all such children, although asymptomatic and even if they do not have a positive history of pica, should have a lead blood determination. The dividends have been shown to be remarkably high. Although at present indoor surfaces are generally painted with nonlead paint, houses which were built more than thirty years ago may contain several coats of paint of a high lead content. Children who live in such houses should be considered as living in a potentially hazardous environment particularly if they exhibit an evidence of pica. It is also well to remember that older houses are not necessarily limited to slum areas and that pica may occur in homes where the paint is not peeling.

During 1963 a total of 335 confirmed cases of lead poisoning were reported to the New York City Poison Control Center of which 7 terminated fatally. By borough, Brooklyn reported a total of 204 cases of which 6 terminated fatally, Manhattan 53 cases, Bronx 51 which included 1 fatality, Queens 53, and 4 were reported from Richmond. Because of our intensified case-finding efforts, more and more cases are being reported from boroughs other than Brooklyn.

About ten years ago there were practically no cases reported from Queens and a very small number from The Bronx and Manhattan. Another evolving observation is that lead poisoning is not restricted to summer months. A large number of cases have been reported this year during the winter months. It would therefore be unwise to let down the lead guard during the wintertime. There is a year-round open season for hunting lead poisoning.

Nortriptyline for treatment of anxiety and depression

Results of a double-blind study of the effectiveness of nortriptyline (Avenyl) in anxiety and depression in 61 patients indicate that this medicine is a useful adjunct in these cases and is particularly valuable for relief of the depressive factor in anxiety states. The total number of patients finishing the study was 61, of whom 47 were given the active drug and 14 were used as controls and received a placebo. Of the treated patients, improvement was rated as excellent in 12, or 25.5 per cent, moderate in 23, or 48.9 per cent, slight in 5, or 10.6 per cent, and zero in 7, or 14.9 per cent. In the placebo group which consisted of 14 patients, none showed improvement.

Writing of this study in a recent issue of the *Journal of the American Geriatrics Society*, Eugene J. Chesrow, M.D., writes that the group consisted of 65 patients, 45 males and 20 females, ranging in age from thirty-four to eighty-seven years. The patients had cerebral arteriosclerosis with or without chronic brain syndrome, generalized arteriosclerosis, multiple sclerosis or other spinal cord disease, various cardiac diseases, chronic alcoholism, and diabetes. Forty-seven of the 61 patients were put on a schedule of 75 mg. of nortriptyline daily. The other 14 were given an identically appearing placebo on the same schedule. The staff was unaware of which medication was active. Most of the subjects in the study were given the nortriptyline for approximately seven months. Noticeable were such signs and symptoms of depression as tension, insomnia, restlessness, hostility, appetite, irritability, and confusion.

Side-effects, when they occurred, were mild and temporary. One patient complained of tightness of the head and depressed feeling, but these disappeared within twenty-four hours without interruption of medication. Two reported mild episodes of vertigo during the first week of therapy, but there was no recurrence. Early in the study, 4 patients had increased nervousness and euphoria, but these disappeared as the study progressed.

Results of the psychologic studies were compatible to the clinical findings. By both clinical and psychologic criteria, findings in the 8 placebo patients subjected to the psychologic tests indicate the lack of effectiveness of the placebo.

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MEDICAL INTELLIGENCE

NUTMEG INTOXICATION*

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WITH the geometric multiplication of drugs available for use in the 1960's and with the corresponding increase in side effects, toxicity and complications, it is refreshing to report anew a toxic state attributable to a common household spice — nutmeg — used since the Middle Ages. Nutmegs were introduced into Europe by the Arabs in the middle of the twelfth century,[1] and poisoning with this spice was probably documented as early as 1576.[2]

Nutmegs are the dried seed kernels of a tall evergreen tree, *Myristica fragrans,* indigenous to the Moluccа Islands of the South Pacific, and now widely cultivated on the Caribbean islands of Grenada and Trinidad. Between 1900 and 1910 the British medical literature contained repeated references to nutmeg poisoning, usually secondary to unsuccessful attempts at abortion; these reports are representative.[2-6] McCord and Jervey[7] recently described an acute case. In the 2 cases presented below, the confessed motivation for ingesting the spice differed from those previously recorded.

CLINICAL SUMMARY

Two male college students, 19 and 20 years of age, were seen in the Student Health Service about 6 hours after each had ingested 2 tablespoonfuls (about 14 gm. or roughly the equivalent of 2 grated nutmegs) of commercially available powdered nutmeg suspended in a glass of milk. This precee-

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dure had been recommended by a "beatnik" acquaintance as providing a mental state somewhat akin to ethanol intoxication, without requiring the use of alcohol.

Approximately 5 hours after swallowing the powdered nutmeg each had the onset of a significant pharmacologic effect, heralded by a leaden feeling in the extremities and a nonchalant, detached mental state described as "unreal" or "dreamlike." Rapid heart rates and palpitation were noted, and both complained of dry mouth and thirst. Onlookers observed that 1 student became quite hyperactive and agitated, and talked incoherently. It was noted that the facies of both were "as red as beets." Nausea, vomiting and abdominal cramps were absent.

Physical examination at this point disclosed 2 hyperactive young men in no acute distress. The skin was quite flushed about the heads and shoulders, but pale and somewhat clammy on the extremities. Pupils were of normal size in 1 and dilated but reactive in the more hypertensive patient. Visual accommodation was not affected. The remainder of the physical examination, including a careful neurologic check, was within normal limits. There were no apparent hallucinations or delusions, but both students were agitated and quite apprehensive throughout the examination. One described a sense of impending doom, as if he were "breaking up inside."

The blood pressures were 170/90 (30 minutes later, 140/84) and 152/84. The pulses were 130 and 148 per minute, and the rhythm strong and regular in both. Temperatures were normal, and the respirations were rapid.

Unfortunately, no initial laboratory studies were obtained. Detailed laboratory studies in the recent case of acute nutmeg poisoning reported by McCord and Jervey[7] were within normal limits. Four weeks after the acute episodes described here, complete blood counts, urinalyses and serum chemical findings — including cholesterol, bilirubin, cephalin flocculation and alkaline phosphatase — were entirely within normal limits.

The initial clinical impression, based upon the history of nutmeg ingestion and the physical findings of flushing, absence of salivation, tachycardia and the dilated pupils seen in 1 patient, was atropine poisoning. Fortunately, the 1st thought — to give pilocarpine — was changed in favor of observation and administration of Epsom salts to empty the bowel of unabsorbed nutmeg.

Extreme drowsiness occurred about 12 hours after ingestion and lasted for the next 24 hours. Both patients stated emphatically that a sense of unreality persisted for 48 to 60 hours from the time of 1 oral dose of nutmeg. Along with decreased salivation, this mental detachment was the last symptom to disappear. Subsequent recovery was uneventful. Regarding the problem of addiction it is pertinent to state that neither would care to repeat this experience, and both described it as unpleasant and somewhat frightening.

Discussion

After early descriptions in pharmacology textbooks of the toxic states associated with the ingestion of nutmeg the literature was sparse for the next fifty years. Dale[3] in 1909, demonstrated that cats were very sensitive to the toxic effects of myristicin, the chief active principle in nutmeg. Central-nervous-system excitation preceding coma and accompanying fatty degeneration of the liver followed feeding of relatively large amounts to cats. Thus, ironically, a "nutmeg liver" resulted from nutmeg poisoning in cats (Fig. 1)! However, in the case reported by Green,[8] biopsy of the liver revealed no pathologic change. Power and Salway,[9] in 1908, had contributed substantially to the pharmacology of nutmeg. Indeed, Dr. Power[10]

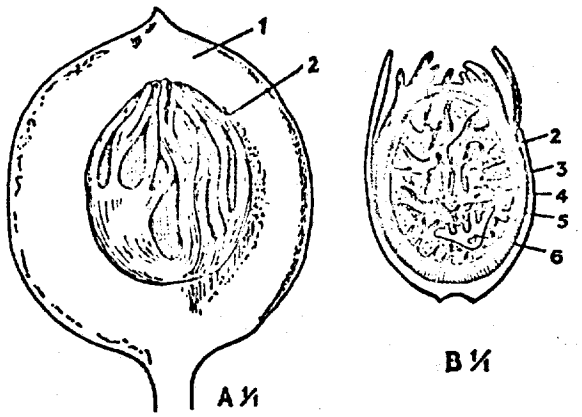

Figure 1. *"Nutmeg Liver" Resulting from Nutmeg Poisoning in Cats (Reproduced from Trease[1] with the Permission of the Publishers).*

A = *the fruit of* Myristica fragrans, *with half the pericarp removed (1), and the aril (2), which in dried form provides the rarer companion spice, mace.*

B = *longitudinal section of nutmeg, showing the reticulated appearance that led to the term "nutmeg liver."*

suggested elsewhere that myristicin alone was not responsible for all the effects of whole nutmeg.

Within the past ten years several scattered references to nutmeg toxicity have appeared in the literature.[7,8,11,12] Symptoms usually appeared three to six hours after the ingestion of one to three whole nutmegs, or 5 to 15 gm. of the grated spice. Striking features common to all these cases, which may be confused with the signs of atropine poisoning, include flushing of the skin, tachycardia, absence of salivation and central-nervous-system excitation. A useful differential clue (not present in the cases reported above but found in most reports) is the early pupillary constriction of myristicin, contrasted with the dilated pupils of the belladonna-type drugs.

An excellent pharmacologic review by Truitt et al.[11] emphasized the bizarre disorder of the central nervous system and pointed out that this effect, which led to the intentional ingestion by the 2 young men described above, was not wholly related to myristicin but to some other volatile principles present in nutmeg. These include eugenol, isoeugenol, geraniol, safrol, borneol and linalool. These writers pointed out the similarity of the structural formula of myristicin, with its indole group, to reserpine and adrenochrome, both serotonin antagonists. Weiss[12] also documented nicely the hallucinogenic and euphoria-inducing effects of nutmeg in prison inmates.

Since the earliest pharmacologic classification of myristicin as an ecbolic oil, or abortifacient, reports in the literature have extensively documented cases of toxicity with uniformly unsuccessful efforts at abortion. Folk medicine has also held that oral ingestion of nutmeg was effective for menorrhagia, boils

and eczema, but the test of time has shown this useful spice to have little medicinal value.

Finally, one wonders if the age-old custom of adding nutmeg to the traditional Yuletide cup of eggnog arose from the psychopharmacologic effect described in these 2 cases.

Summary and Conclusions

Two cases of nutmeg poisoning are reported in college students who took the powdered spice to produce a sense of exhilaration and intoxication. Apparently, this odd pharmacologic effect is fairly well known among the more bohemian elements of the population, as well as alcoholic patients and narcotic addicts whose regular supplies are exhausted. The clinical findings and courses are briefly described. These cases are reported as an interesting example of toxicity caused by a usually benign household condiment.

I am indebted to Dr. Edward McG. Hedgpeth, director of the Student Health Service at the University of North Carolina, for giving me the opportunity to see these 2 patients and for his co-operation in the preparation of this report.

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ACCIDENTAL GLUTETHIMIDE INTOXICATION IN CHILDREN*

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Glutethimide is a sedative and hypnotic drug that has gained widespread use since its introduction in 1955. When used in therapeutic doses it appears to be relatively free of adverse effects. However, its margin of safety is rather narrow, coma having resulted in adults from as little as ten times the therapeutic dose.[1] Recently, an unusual neurologic syndrome manifested by cerebellar ataxia, nystagmus, dilated pupils and rapid fluctuations in state of consciousness was observed in 2 children who accidentally ingested only two to four times the therapeutic dose of glutethimide.

Case Reports

Case 1. A 6-year-old girl was admitted to the Children's Hospital Medical Center, Boston, on June 19, 1961, because of drowsiness and ataxia. Three days earlier she had fallen off a fire hydrant and had struck her head in the occipital region. She was not concussed. On the evening before admission unsteadiness of gait was noted. The next morning she was drowsy, and during the ensuing hours several episodes of deep sleep were observed. When aroused, she was unable to sit or stand. There was no vomiting or complaint of headache. The child had been taking penicillin tablets by mouth twice daily for rheumatic-fever prophylaxis. A bottle of glutethimide,‡ containing 500 mg., had been kept next to the penicillin tablets. The mother reported that 1 tablet of the former might have been given by mistake on the afternoon before and 1 on the morning of admission.

On examination the patient's mental status varied from stupor to mild drowsiness. The patient weighed 18.1 kg. The mucous membranes were dry. Both pupils were widely dilated and reacted sluggishly to light. There was marked horizontal nystagmus on lateral gaze in both directions. Vertical nystagmus on upward gaze was noted on 1 occasion. Muscle tone was diminished. There was marked truncal ataxia, the child being unable to sit or stand. Intention tremor of the hands was present bilaterally. Tendon reflexes were hypoactive, and plantar responses were flexor. The response to pinprick was generally diminished.

The temperature was 99.6°F., and the pulse 76 per minute. The blood pressure was 110 systolic, 60 diastolic.

No fracture was observed on roentgenograms of the skull. An electroencephalogram obtained while the patient was stuporous showed an excessive amount of diffusely fast activity (20 to 30 per second), suggesting drug intoxication. The glutethimide blood level, determined by a modification of the method of Goldbaum,[3] was 0.7 mg. per 100 ml. 6 hours after the assumed ingestion of the 2d 500-mg. tablet. The cerebrospinal fluid was clear and under a pressure of 180 mm.

The child improved rapidly. On the next day she was only mildly drowsy and was able to walk. A slight intention tremor and nystagmus were still present, but had cleared completely over the next 24 hours.

Case 2. A 5-7/12-year-old boy (M.G.H. 120-07-78) was admitted to the Massachusetts General Hospital on August 9, 1962, because of lethargy and ataxia. He had been in good health until the afternoon of admission, when he fell from his tricycle. Upon arising he staggered wildly and had to be carried home. He complained of feeling dizzy. The family physician found him to be lethargic and unsteady on his feet and referred him to the hospital.

On admission the patient was awake and euphoric. His speech was slurred. The weight was 18.9 kg. Both pupils were widely dilated and reacted sluggishly to light. Coarse horizontal nystagmus on right lateral gaze and vertical nystagmus on upward gaze were present. There was truncal ataxia, the patient being unable to sit without support. Past pointing and marked unsteadiness were present on finger-to-nose and heel-to-shin testing. The tendon reflexes were symmetrically hypoactive, and the plantar responses were flexor. X-ray films of the skull showed no fracture.

The temperature was 99.2°F., and the pulse 88. The blood pressure was 120/80.

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‡In the form of Doriden, Ciba Pharmaceutical Company, Summit, New Jersey.

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NUTMEG POISONING

D. R. Rellan

Nutmeg is, at present, used mostly as a flavouring agent. Towards the end of the last century it gained an undeserved reputation as an abortifacient. It has also been used as a soporofic agent and as a lotion for hair, said to have stimulating and anti-parasitic properties. In recent years there have been a few reports of poisoning following its use as a euphoria-inducing agent.[17, 11] The following is the case report of a patient who consumed nutmeg with the intention of experiencing a sensation of exhiliration. Instead he became drowsy and had a generalised clonic convulsion.

CASE REPORT

The patient, a 22-year-old male Caucasian, consumed half an ounce of nutmeg powder with milk on a Saturday evening, having learnt from his friends that nutmeg makes one "feel at the top of the world". He had never taken nutmeg before except as a condiment with rice pudding. Instead of feeling elated, he felt depressed and went to bed at 11.30 p.m. He was drowsy throughout Sunday and could not be induced to get up until 6.0 p.m. He then experienced a feeling of nausea, diplopia and blurring of vision. He felt faint and had to sit down, after which a generalised clonic convulsion lasting for about a minute was observed by his parents. He was unconscious for two or three minutes. He was brought to the Casualty Department at Weymouth and District Hospital in a drowsy state and was admitted for observation. His face was flushed; otherwise the physical examination did not reveal any abnormality. On Monday morning (36 hours after ingestion of nutmeg) he was still quite drowsy. By the evening he was quite normal. He made an uneventful recovery and described the experience as unpleasant.

The patient appeared to be a stable person and denied any difficulty with his work or social life. No history of addiction was obtained; he was moderate in smoking and drinking.

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DISCUSSION

Pharmacological Aspects

Nutmeg consists of the dried kernels of the seeds of Myristica Fragrans Hoʻtt (fam. Myristicasae), a tree indigenous to the Mollucas and cultivated in Penang, Sumatra, and the East and West Indies. It contains about 5 to 15% of volatile oil and about 35% of solid fat, the chief constituents of which are myristic acid (about 60%) and smaller amounts of palmitic, oleic, linoleic and lauric acids.[2] Toxity of nutmeg is associated with its volatile constituents, and of these, myristicin, forming some 4% of the oil is thought to be the poisonous principle. Wallace, working with Cushny[3], demonstrated that frogs placed in a dilute watery solution of myristicin manifested restlessness (probably from irritant action on skin) followed by depression, paralysis and abolition of reflexes. This resembles symptoms in many patients of nutmeg poisoning — i.e. depression of central nervous system with some indication of stimulation. Dale,[4] using grated nutmegs as well as chemically pure myristicin, demonstrated advanced fatty degeneration in cats. Power[13] found that a proportionately greater dose of myristicin was required to produce the effects of nutmeg and suggested that the symptoms of

nutmeg were not entirely due to myristicin. This is supported by the work of Truitt *et al.*,[16] who found that the ingestion of myristin did not reproduce the character or intensity of response elicited by ground nutmeg and have suggested that the other volatile constituents (safrol, borneol, linalool, eugenol, isoeugenol and geraniol) in nutmeg contribute markedly to its psychopharmacological effects. One of the authors ingested 15 gm of nutmeg to study its effects. The symptoms and signs observed were vasomotor instability, tachycardia, hypothermia, absence of saliva, constricted pupils, emotional liability and inability to think clearly.

Clinical Aspects

Towards the beginning of this century there were a number of reports[15, 12, 7, 1, 19] of nutmeg poisoning in the British literature, following its use as an abortifacient. It was, as a rule, unsuccessful as an abortifacient except in a case reported by Hamilton[7] when abortion followed a month afterwards (probably unrelated to nutmeg). Other earlier reports of nutmeg poisoning include those following its use as a treatment for menstrual irregularity[8] and as a flavouring agent for pudding.[6] Cushy[3] presented an excellent review of the subject. The amount consumed in most of these cases was one to one-and-a-half grated or finely cut nutmeg. The effect in many of them was narcosis, varied by excitement and delirium, commencing a few hours after ingestion and usually followed by recovery after 24 hours. Other features include pupillary dilatation,[12] collapse,[15] cyanosis, flushed face and fear of death,[5, 7] choreic symptoms,[18] and abdominal pain.[19] Cushny described a fatal case of poisoning in an eight year old boy.

McCord and Jervey[10] described acute anxiety reaction in a man who consumed nutmeg as the treatment for a pustule on his neck. Rees[14] recently reported mild toxic psychosis in a woman who had the habit of nibbling nutmegs. Green[5] described a case of a patient who became disoriented and delirious after taking 18 grams of finely ground nutmeg in an effort to induce menstruation.

Alleged Euphoria-inducing Action of Nutmeg

Powdered mysistica (nutmeg) is included among the prison inmates' repertory of alleged euphoria-inducing drugs. Weiss[17] studied ten cases among prison inmates who used nutmeg for this purpose. In nine of these ten cases, their primary objective was achieved. A feeling of being transformed aloft was experienced, accompanied by drowsiness in some cases and excitement in others. Verbal reports about the effect of nutmeg were: "As far as the world's concerned, you don't care about nothing. That's a day I don't know I'm in this place (prison)": "don't give a damn": ".... Your own and other people's problems do not worry you". One of them, however, developed toxic psychosis. The effects were considered to be essentially similar to those of marijuana, although comparison with heroin and alcohol were also cited. Payne[11] has described cases of two college students who took nutmeg for its alleged euphoria-inducing effect. Their symptoms were leaden feeling in extremities, unreal mental state, hyperactivity, tachycardia, extreme drowsiness, after 12 hours, lasting for twenty-four hours. Both of them considered the experience as unpleasant and frightening. According to Payne, the euphoria-producing effect of nutmeg is fairly well known among the more

Bohemian elements of population as well as alcoholic patients and narcotic addicts whose regular supplies are exhausted. Potentially it belongs to the same class as marijuana, cocaine, heroine, "purple hearts" and other drugs used to induce a sensation of elation. Unauthorised sale of many such "drugs" is illegal. Nutmeg being an ingredient of spices is quite easy to obtain. It is also quite cheap: retail price of 1 oz of ground nutmeg is 1s. 3d. The patient reported in this communication consumed only half of this amount. The same is true of many other case reports.

SUMMARY

A 22-year old male patient consumed nutmeg with an intention to experience a sensation of exhilaration. He felt depressed and was drowsy for 36 hours. He had a clonic convulsion for about one minute and was unconscious for a few minutes.

The pharmacology of nutmeg is outlined. Earlier reports of nutmeg poisoning are reviewed. The implications of its use as an intoxicant are discussed.

ACKNOWLEDGMENT

I am grateful to Dr. P. Hughes, under whose care the patient was admitted, for permission to publish the case and for his advice.

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SPECIAL ARTICLES

Illicit Drug Use Among Canadian Youth: Part I

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THE incidence of illicit drug use among Canadian youth is high enough to cause serious concern among the medical, educational and law-enforcement professions. In the period from January 1, 1967, to October 31, 1967, there were close to 1300 arrests and 359 convictions related to marijuana;[20] this represents an increase of over 300% when compared to 1966. The median age of the persons involved was about 17 years. In some Winnipeg schools during the fall of 1967 the incidence of glue-sniffing was estimated to be between 2 and 5%.[18] A Canadian magazine[7] estimates that around 20% of Canadian university students have had experience with marijuana, and this figure corresponds to estimates quoted for English[12] and American universities. The World Health Organization considers the abuse of amphetamines to have reached epidemic proportions, and North American studies seem to support this viewpoint.[23, 27] The Canadian situation is considered grave enough for public health and educational authorities in Toronto, Vancouver, Winnipeg and Ottawa to initiate school and other programs concerning the dangers and characteristics of the various drugs.

It is impossible at the present time to give an accurate figure for the incidence of drug experimentation and abuse in North America. The issue is greatly confused by the inaccurate statements and sensationalism of the communications media, by the "underground" nature of the traffic and indulgence in the drugs, and by the tendency of the young people themselves either to understate their knowledge of local incidence through fear of incrimination or to overstate the figure for purposes of self-aggrandizement—one often has to take a grain of salt for every micro- or milligram of drug claimed to have been ingested. It should be appreciated that the majority of youthful drug users do not come to the attention of the medical profession, for a variety of reasons: (1) fear of detection and punishment; (2) the rejection of physicians as prototypes of the middle-class society against which the "hippie" community is allegedly in revolt; and (3) the ready availability of antidotes (such as chlorpromazine and barbiturates) from illicit distributors and from many habitual users themselves.

It can be accurately stated that the drugs to be discussed are quite freely available in Canadian cities. The situation is such that each young person must decide whether or not he will try a particular drug, for he will almost certainly have the chance. Distributors ("pushers") are in contact with the student population of most high schools and universities, and frequent the coffee-houses and restaurants popular among teenagers. The "pushers" themselves are mainly youths who are taking serious legal risks, primarily because of the astounding profit to be made from the sale of these drugs. (It has been estimated that a dose of LSD sold illicitly for 10 dollars would be worth nine cents if produced commercially.)

The sociocultural background of the involved young people is essentially affluent middle-class and well-educated, as contrasted to the socially disadvantaged youths who were the subjects of earlier reports about adolescent drug abuse.[2, 16] Though no adequate studies have yet been reported, the incidence of delinquency (apart from illicit drug use) seems to be low for the marijuana and psychedelic users. The glue-sniffing population tends to have a high association with reported delinquency and school failure.[6, 40] It is a mistake to presume that the majority of drug users are to be found among the "hippie" communities. Especially in the case of marijuana, the user can be in appearance any variety of Canadian youth. For useful discussions on the ethos surrounding the illicit use of psychoactive drugs, the reader is referred to Taylor,[45] Kline[25] and Freedman.[17]

All of the drugs to be discussed could loosely be called "hallucinogens"—though in fact actual hallucinations are far less common than claimed,

Part II will be published in the issue of March 2.

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most of the perceptual distortions being in the nature of illusions. The manifestations of any of these drugs in a particular person are strongly influenced by set (anticipation), setting and suggestibility. It is hoped that this article will help the physician recognize what is fact, hypothesis, myth or controversy with regard to the various drugs of which he hears and reads, and particularly when he is confronted with a non-alcoholically intoxicated adolescent. The true narcotic drugs will not be discussed in detail as they are not as yet of significance to this age group.

SOLVENT INHALATION

The term "solvent inhalation" is preferable to the more commonly used "glue-sniffing", as the inhalation of a variety of volatile organic solvents is (and has been for some time) in vogue among younger teenagers, the aim and effect being to produce transient intoxication and elation. The deliberate use of such solvents has reached epidemic proportions in the U.S.A., and is causing concern in Canada.[18] The Federal Government is now moving to impose restrictions on the sale and use of model airplane glue and other substances containing volatile solvents.

Commercially (and legally) available products in common use by thrill-seeking younger adolescents include:

1. *Glues or cements:* the most popular source of solvents for teenagers, especially plastic (styrene) cements, model cements and household cements. The principal solvents in these glues are toluene and acetone.

2. *Fingernail polish remover,* containing primarily acetone, alcohol and aliphatic acetates.

3. *Lighter fluid, cleaning fluid and gasoline,* containing naphtha, benzene and sometimes carbon tetrachloride.

4. *Lacquer thinners,* containing toluene and aliphatic acetates.

5. *Ether.*

It would appear that any volatile solvent possessing the property of lipid solubility can produce intoxication similar to that produced by the above-listed agents. The beginning "sniffer" is particularly liable to experiment with any variety of substances to find his own preferred source.[40]

The usual method of use is to place the solvent-containing substance in a plastic bag, and then insert the face into the opening for inhalation. An allied technique is to place the substance in a tightly rolled handkerchief or piece of rag which is then held against the mouth or nose and sniffed (and sometimes sucked). The odour of the solvent is usually noticeable on the breath and clothes of the user, and the discovery of plastic bags, handkerchiefs or rags containing dried glue or other substance should alert parents to the probability of solvent inhalation. Users who suck or sniff the solvent through cloth may display erosion of the gums or nasal mucosa.

The clinical picture produced by the various solvents tends to be fairly constant; toluene is the most popular substance sought, the concentration obtained from one tube of polystyrene cement being up to 50 times the maximum allowed in industrial operations.[40] With some variation according to type and concentration of solvent used, there is, within minutes of inhalation, euphoria, slurred speech, feelings of dizziness and floating, confusion, and a sense of reckless omnipotence which may give rise to impulsive acts resulting in accidents or antisocial and self-destructive behaviour;[6, 40] vivid visual, and less commonly auditory, hallucinations may occur in particularly susceptible subjects. This phase of intoxication lasts 45 to 60 minutes, and is followed by drowsiness lasting up to one hour. There is commonly a patchy amnesia for the period of intoxication. With inhalation of higher concentrations, stupor and even convulsions or loss of consciousness may supervene. Abnormalities of the electroencephalogram are found during the phase of intoxication and may persist for several weeks after cessation of inhalation. Marked anorexia is frequent with repeated use of the solvent. Transient abnormalities of renal functioning are the most constant findings on laboratory investigation, isolated reports of hepatic and bone marrow malfunctioning exist, but there is no established evidence of permanent brain damage.

Most deaths related to solvent inhalation have been due to suffocation by the plastic bags used; the small number of reported deaths not due to this method of suffocation have been found to be associated with pulmonary edema or hemorrhage in alveolae.

These solvents are definitely productive of tolerance and psychological dependence. The youth who commences with, say, one tube of glue may find after several months that he has to double, then triple, the number of tubes to obtain the same degree of intoxication. Psychological dependence is evidenced by a determined search for substitutes should the [illegible] have access to his preferred source [illegible] degree of recidivism, and by a cor[illegible] inhale solvents which occurs in mo[illegible] sniffers. Physical dependence has not as [illegible] adequately demonstrated.

PSYCHEDELIC DRUGS

The psychedelic ("mind-manifesting") drugs most commonly used are, in order of increasing potency, DMT, LSD and STP. Variants in less common use include psilocybin, mescaline and such exotics as nutmeg and morning-glory seeds. Some of these drugs are known to contain indoles or have amphetamine-like structures. One of the postulated biochemical modes of action involves interference with the metabolism of the catecholamines or serotonin. The primary neurophysiological impact is thought to be on the afferent impulses entering the ascending reticular system through collaterals from the sensory pathways.[5] The psychological and somatic effects of LSD can be used as a model for all of these psychedelic drugs; such variations as occur with the others are in terms of frequency and intensity of the basic LSD phenomena.

LSD-25

Lysergic acid diethylamide ("acid"), the most commonly used of these preparations, is a semisynthetic derivative of the fungus ergot of rye. It is one of the most potent psychochemicals known, a dose so small as to measure no more than 1/700 millionth of the weight of an average male being adequate to yield significant intoxication. One ounce of the substance could "turn on", i.e., render psychotic, a city of 300,000 inhabitants.[33] In solution, LSD is a colourless, odourless liquid, so that detection can be difficult. During the early days of the psychedelic movement several drops of the dissolved white, crystalline powder of LSD were added to blotting paper or sugar cubes, which were then sucked or swallowed. A common method for transporting the substance undetected was to soak a handkerchief in the solution, allow the liquid part to evaporate, and then carry in a pocket the impregnated handkerchief which could be later cut into squares for sale.

Currently the drug is distributed ("pushed") mainly in tablet form or in capsules, the contents of which vary widely in potency and purity. A minimum of 50 to 150 micrograms of LSD may induce a psychedelic experience ("trip"), depending on the sensitivity and experience of the subject; experienced users ("acid-heads") may ingest ("drop") a single dose of several hundred (and uncommonly several thousand) micrograms—increased dosage leads to prolongation rather than intensification of the symptoms. Tolerance develops and disappears rapidly, and there is no evidence of physical dependency or significant abstinence symptoms.

The symptoms and signs of LSD intoxication begin to appear about 30 minutes after ingestion, and last, for the average dose, 10 to 12 hours. Autonomic effects include heightened blood pressure and dilated pupils (with consequent risk of glaucoma in susceptible subjects). Certain of the psychological phenomena[11, 42] are invariant, occurring whenever an effective dose is taken. Thus there are alterations of perception such as derealization and depersonalization, with a peculiar splitting of the ego into the detached, observing self and the involved, experiencing self; visual (and less commonly auditory) illusions—rarely true hallucinations—involve colour, size, shape and apparent plasticity. Thought processes are disturbed, with difficulty in concentration, vagueness, pressure of ideas, and a firm belief that the subject has attained an intellectual brilliance approaching genius, with attendant stunning insight into his own personality and a conviction that the dilemma of existence and earthly suffering has been solved. As Leary[29] has commented, "You have to go out of your mind to use your head." Regrettably, the alleged insights and growth of personality do not often stand up to unprejudiced investigation, nor are they usually applied to the on-going life of the non-intoxicated user; some of the derived solutions to social and world problems may be absorbed into (or perhaps suggested by) the general philosophy of the psychedelic cult ("turn on, tune in, drop out", "make love, not war", etc.).

The individual may be so withdrawn into his experiences, or so fixedly intrigued by the distortion of perception, that he appears to be in a state approaching catatonic stupor. On the other hand, hyperactive behaviour may supervene. The subject is, however, generally responsive to the intercession of another person, and his attention can, with persistence, be obtained. The whole psychedelic experience is later remembered with intense clarity and recognized as having been a paranormal phenomenon.

Less constant responses, depending very much on anticipation, the setting and suggestibility, include affective responses ranging from exhilaration and ecstasy to panic or despair. Contrary to popular belief, the proper preparation of a subject and the presence of an experienced, sympathetic "guide" do not guarantee a satisfying experience, and one cannot predict the quality of a particular "trip" for any given person. Other less invariant effects include the actual type of ideational content and the uncommon attainment of a mystical transcendental state with consequent rapid personality change—the latter is uncommon outside of a psychotherapeutic setting, in which insights are worked through and integrated into the personality. The

reported successful treatment of such conditions as alcoholism and homosexuality does not necessarily involve the attainment of such a transcendental state. Certainly, for the majority of young people using LSD illicitly, one does not often see evidence of personality growth and maturation. A study of the long-lasting effects of LSD on normals[35] indicated that, while "58% of the subjects subjectively reported some lasting effects after 6 months, . . . attempts to measure these changes via psychological tests provided only minimal supportive evidence". LSD has not been adequately demonstrated to increase creativity, nor do most experts feel that it is a valid or reliable pathway to mystical or religious experiences.[45]

Several studies[44, 45, 49] have adequately demonstrated that LSD must be regarded as a dangerous drug with potentially serious complications. Untoward effects reported include irresponsible and dangerous behaviour during the intoxication, suicidal depression during or sometimes following the psychedelic state after an interval, short-lived psychoses (usually of a paranoid type) requiring hospitalization, prolonged anxiety states, and the precipitation in predisposed individuals of schizophrenic reactions. Reports of homicide are rare but do exist. Recurrence of the psychedelic experience ("splashers" —a type of echo phenomenon) may occur any time up to a year after the last dose of LSD, without further ingestion of the drug. They are particularly prone to occur if the subject takes another drug such as marijuana or amphetamine.

Recent reports raise the strong possibility that LSD may have detrimental somatic effects. Convulsions have been reported[44] and the risk of chronic brain damage after several hundred "trips" has been suspected but not yet firmly established. Initial reports of chromosomal abnormalities[8] have since been confirmed by some independent investigators and contradicted by others.[31] No confirmed evidence exists at the time of writing of congenital abnormalities in the offspring of *humans*, but it is doubtful, in view of the recent thalidomide disaster, whether any physician will now use LSD on human subjects until the matter is clarified. There is at present no firm knowledge of which factors, such as dosage or frequency of use, may be related to somatic complications.

DMT

Dimethyltryptamine is prepared as a liquid into which parsley, tobacco or marijuana is then dipped and smoked in a pipe. The effects are similar to but usually milder than those of LSD and last only about 30 minutes.[33] DMT tends to give a greater proportion and variety of visual illusions, and there are greater (though short-lived) autonomic effects. The rapid onset of the psychedelic experience and the sense of complete loss of control can lead to panic states much faster than LSD,[22] especially if the drug is injected intramuscularly, which is uncommon.

STP

The letters stand for Serenity, Tranquillity and Peace—and any associations with a tombstone may not be inappropriate in view of the occasional fatal outcome of STP ingestion (no deaths have been directly attributed to the physiological effects of LSD). The formula, 4-methyl-2, 5-dimethoxy-alpha-methylphenethylamine, relates it to both mescaline and the amphetamines.[41] Distributed in the form of blue or orange tablets, it is a synthetic substance which is considerably more potent than LSD—it has been called a "megahallucinogen" and the effective dose is said to be 10 micrograms.

The actual psychedelic experience lasts for four to five days, with effects similar to though much more intense than those of LSD. The subject is unable to sleep for the first 20 hours or so, then sleeps for 4 to 10 hours; on awakening he finds himself in an even more intense psychedelic experience than before sleep, and the effects are highest at this time, gradually wearing off in the next few days and leaving the subject exhausted.

The chances of complications are greatly increased, and symptoms similar to those of atropine poisoning are frequent—dryness of the mouth, dysphagia, abdominal discomfort, blurred vision, etc. Pupils are greatly dilated, the skin is flushed and there is tachycardia. Delirium and fever may also be present. Deaths have been reported following respiratory failure or convulsions. In addition, use of the antidotes ("downers") appropriate to LSD ill-effects, particularly phenothiazines, has intensified the toxic symptoms of STP and has, in a few cases, been fatal.[41]

Little else is known about this drug. It is not at present widely used for fear of the consequences—public education may have deterred wide experimentation, in contrast to the history of LSD. Even the "hippie" community warns against its use by any but the experienced LSD user.

OTHER PSYCHEDELIC PREPARATIONS

Nutmeg (Myristica fragrans) has long been used by prisoners and sailors for its psychedelic properties, but has until recently escaped the

attention of inquisitive young minds. Its use is now spreading in North American high-school and college campuses,[30] though not yet to any great extent in Canada. The principal psychoactive component is thought to be contained in myristicin, a component of the aromatic fraction of the spice with structural similarities to mescaline and ephedrine.[46] Dose is from one teaspoon to the contents of a whole can of ground nutmeg, the spice being swallowed in a glass of water, juice or milk. It has also been sniffed. From two to five hours after ingestion the subject begins to undergo a psychedelic experience, with less frequent visual illusions than LSD, greater intensity of derealization and depersonalization, a sense of floating, and feelings of aloneness. There is usually accompanying pronounced malaise, headache, dry mouth, dizziness and abdominal discomfort. The effects of a single dose pass off after 12 to 24 hours.

Morning-glory seeds contain two alkaloids of lysergic acid—lysergic acid amide and isolysergic amide. Only two varieties of the plant (Convolvulacea) produce seeds with these psychoactive substances; other varieties can contain dangerous amounts of toxic ergot derivatives.[39] The two varieties of seeds used by teenagers are called "Heavenly Blue" and "Pearly Gates". The ingestion of these seeds, often prepared as a solution, has become less common since agricultural authorities began to spray them with insecticides and nauseating chemicals to discourage their use as intoxicating agents. The symptoms[14] are similar to those of LSD, though of lesser intensity and so variable as to be frequently disappointing to the user.

Psilocybin, like LSD an indole derivative, has milder effects than LSD[39] and is not in wide use. *Mescaline* is no longer popular because its more pronounced autonomic effects render it less pleasant than LSD. *Bananadine*, the alleged psychedelic constituent of banana skins ("mellow yellow"), contains no psychoactive agents;[4] any effects are purely the result of suggestion.

AMPHETAMINES

The abuse of amphetamines ("speed") is thought by the World Health Organization to have reached epidemic proportions, and there is reason to believe that this group of stimulants presents a serious problem in the U.S.A.[27] and Canada.[23, 20] While traditionally amphetamine abuse has been associated with its prescription for obesity, fatigue and depression,[10] the current upsurge is due essentially to the use of amphetamines as excitants and thrill-inducers by the same groups of young people who are devotees of marijuana and LSD. Most commonly the amphetamines, particularly methedrine, are used in this context in conjunction with LSD. Methedrine prolongs and intensifies the LSD experience, and may even reactivate it, in regular users, without recourse to further LSD. Less commonly methedrine is used alone for its stimulant and psychotogenic properties—usually in tablet form, but also as a powder (which is sniffed) and increasingly by intravenous injection ("mainlining").[27] The increasingly high incidence of infectious hepatitis in the "hippie" communities is thought to be the result of the communal use of non-sterile needles and syringes. The use of inhalers containing amphetamines is less popular than previously. The use of amphetamines has, of course, long been common among students facing a final exam.

Initial doses are in the order of 10 to 20 mg. orally and 20 to 40 mg. intravenously. The results are a sense of well-being and euphoria, absence of fatigue, a reduction of appetite, a compulsion to talk and move about, and irritability. Sleeplessness is common, and with sustained or recurrent use there is usually a rebound depression as the effects wear off. The amphetamines are somewhat unique among central nervous system stimulants in their capacity to produce a gradual and increasing tolerance.[11, 43] Thus the habitual user may eventually be taking single oral doses of 150 to 250 mg. per day, or single intravenous doses of 100 to 300 mg.[27] With these larger doses and with continued abuse the appearance of paranoid attitudes is almost universal. There may be marked loss of weight, non-healing ulcers, brittle fingernails and tooth grinding.[27] The larger intravenous doses are particularly liable to result in disorganized behaviour, hallucinations and the acting-out of paranoid ideas—amphetamine psychosis. Recent reports of violence and homicide within the "hippie" communities in the U.S.A. are related to the increasing use of large doses of methedrine—hence the lapel buttons warning that "speed kills".

Amphetamine psychosis is a recognized clinical entity.[10] Even a single therapeutic dose may, in susceptible individuals, produce a paranoid psychosis indistinguishable from alcoholic hallucinosis or paranoid schizophrenia. The clinical picture is "a paranoid psychosis with ideas of reference, delusions of persecution, auditory and visual hallucinations, in a setting of clear consciousness".[10] Patients recover within a week of withdrawal, during which time there are periods of prolonged deep sleep, followed by marked hunger for food and depression which may lead to suicidal attempts; amphetamine is present in

the urine for up to seven days after withdrawal, and Connell[10] recommends the use of a modified methyl orange test whenever the question of amphetamine use arises. Dependency of the amphetamine type may, in the absence of psychotic symptoms, present as a chronic anxiety reaction.

Amphetamine abuse is associated with marked tolerance and variable but very frequent psychological dependency. Though Eddy *et al.*[11] contend that amphetamine abuse is not associated with physical dependence or a characteristic abstinence syndrome, other authors[10, 27] believe that the depth and length of the withdrawal sleep and the marked hunger for food on awakening point to an abstinence syndrome. Oswald and Thacore[37] have demonstrated what they regard as physiological dependence in their studies of the electroencephalographic sleep patterns during the withdrawal phase: "In each case upon withdrawal a huge increase in the R.E.M.-time occurred, reversible by reinstituting the drug." It may take up to eight weeks for the electroencephalographic sleep pattern to return to normal.

Central nervous system stimulants in less common use include ephedrine and methylphenidate; their effects and dangers are similar to the amphetamines but less pronounced.

REFERENCES

The references for both Parts I and II will be published with Part II in the issue of March 2.

Hallucinogenic Drug Abuse:

Manifestations and Management

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THE recent plea by Smart and Bateman[1] for added information about the growing illicit use of hallucinogens points up the paucity of literature pertinent to the present nature of the problem and the management of acute situations. To help meet this need, we believe it is worth reporting the experiences and impressions which we have gained over the past seven years through our contact with persons using hallucinogenic drugs in a medical setting involving clinical experimentation and treatment, and, more recently, in the emergency department and in the community outside the hospital. As a guide to health resource personnel who are likely to encounter these situations in growing numbers if they have not already done so, we would first like to discuss the clinical presentations and management of these problems. Further information, growing out of our investigations, and related to such questions as motivation of drug users, frequency and pattern of such drug intake and apparent incidence and nature of unfavourable reactions, is in preparation.

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PRESENTING CLINICAL FEATURES AND MANAGEMENT

1. *Commonly Available Hallucinogenic Drugs*

Lysergic Acid Diethylamide (LSD)

When first seen, the patient is commonly in a state of acute distress with fear and anxiety but with a relatively clear sensorium. Visual and tactile hallucinations, often accompanied by synesthesias, are common. The patient is sensitive to external stimuli, often of a minor nature, and his focus of attention may shift quickly and frequently. Paranoid suspicions and interpretations are prone to occur, and autistic withdrawal may be noted. As the patient has turned to drugs as a partial attempt to resolve his problems, his fear in the acutely psychotic state is frequently of further and continuing loss of control over his already shaken mental capacities to cope and adapt. This fear may be the basis for the development of his paranoid mistrust and ideation. There is a conspicuous tendency for the mental state to vary considerably through periods of apparent lucidity and normalcy to sudden recurrences of the bizarre or fearful state.

The Use of Nutmeg as a Psychotropic Drug

Report of Two Cases

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THE NUTMEG COMPLEX

WITH the increasing cost and difficulty of procuring heroin and the fear of its use, many in recent years who desire to use drugs to produce a 'kick' resort to other substances. Among those allegedly utilized have been nutmeg, banana peel, glue, L.S.D. and "aspirin and coke with gin."

In this study two cases of the use of nutmeg for this purpose are reported (nutmeg complex).

CASE REPORTS

CASE I: R. G., a 30-year-old laborer was told of the use of nutmeg to produce a "happy feeling" by a friend. He stated that he had heard that the use of nutmeg would also "give the kick of a mule," if well mixed. Accordingly he used a small can of nutmeg, poured the same into a bowl and then added a glass of grapefruit juice and half a glass of coke. Using an eggbeater to mix this concoction, he soon had it prepared for drinking. Then, before three friends, who looked on with curiosity, he drank a glass of the mixture and subsequently another half glass.

About two hours later he first experienced great thirst. Yet, when he saw water he seemed afraid to drink it. After drinking one half glass of water, all objects in the room seemed to be swaying slightly. Color of objects seemed deeper and he seemed to be swaying. He thought these conditions were unreal, yet he felt they were happening at the same time. Confused, he went to bed and pulled the pillow over his head, but he was too restless to stay in this position long because he felt "so hot." Then he seemed as though he had to lift his legs higher as he walked. Gradually he realized he did not know what he was doing. He called his wife who called some of his friends to stay with him and to help, if necessary, because she had become frightened.

At this stage he appeared nauseated and talked incessantly. At intervals he seemed quite happy, elated and amorous and, every now and then, stopped as though he was listening to something. By this time he reported being "light-headed," as if floating, with some vague abdominal pains. This experience had now gone on for several hours. At this stage he was given some weak salt water to make him vomit, since it was believed that he had been drinking and this might help as a gastric lavage. He stated that he was told that he did not vomit but soon fell into a heavy sleep. He awakened about six hours later with a strange feeling as if he were not quite real, as if he had been in a "trance." For the next eight hours he felt that he wanted to cry, but could not. He became depressed and slowly drank some warm milk. He showed evidence of tremors some 48 hours later, but gradually felt better.

CASE II: K. M., a 23-year-old brick-layer decided to try the same experience of his friend, because it sounded fantastic and unreal. Taking a small can of nutmeg, he mixed it with grapefruit juice and ginger-ale. The exact amounts he did not determine. He drank two full glasses and then decided to go home that evening and go to bed. In bed he had the sense that the bed was moving with him so that he got out and sat in a chair. He had auditory and visual hallucinations, became restless and was unable to sleep. The color of things seemed deeper—dark objects seemed darker and white seemed whiter. He lost his appetite. He was afraid to drink water and became fearful of everything. His mouth was parched. His father was called. His eyes were reddened. He had not eaten and his hallucinatory experience had increased.

Hospitalization was advised, and he was restrained forcibly. The heart rate was rapid, 140 per minute and the skin was warm. The blood pressure was $\frac{140.}{70}$ The reflexes were lively, but no Babinski was present. The patient was given fluids daily for three days, which included 2000 cc. of 5% glucose in normal saline. A chelating agent, calcium versenate was given daily for two days. After the fluids, the patient recovered from this ordeal in four days.

COMMENT

The use of nutmeg as a psychotropic substance was reported by Weil and Shulgin.[1] Symptoms similar to those reported were also noted by McCord,[2] who described symptoms of restlessness, dizziness, fear of death, coldness of extremities, precardial and abdominal pain. Deliriousness, dyspnea, rapid pulse and increased body temperature were also noted. Many or these symptoms were noted in our patients. That this substance makes patients "get high" and thus give rise to intoxication has been reported by Payne,[3] who reported cases.

In his autobiography Malcolm X[4] reported that while in prison he used nutmeg in water and found it had the "kick" of three or four reefers.

These data and many others have proved that nutmeg can be, and is a dangerous drug. It has been known to produce death in large enough doses.[5]

SUMMARY

Two instances of patients using nutmeg have been reported. Symptoms of restlessness, delirium, warmness of the body, abdominal and chest pains, hallucinations and delusions were the predominant manifestations.

While this drug is much cheaper for use and probably less dangerous than the habit-forming heroin, it must be stated that it is not free from danger and may cause death.

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Hallucinogenic Effects of Nutmeg in Adolescent

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THE HOUSEHOLD SPICE, nutmeg, has been known to have psychotropic effects. These have been described in varying details by a number of reports in the literature. Even authors who do not accord them much prominence, such as Payne,[1] do mention them. It is generally assumed that the active psychotropic substance is myristicin. The inability to imitate nutmeg intoxication with synthetic myristicin has given rise to speculation that other substances of the volatile oil obtained from the nutmeg seed, Myristica fragrans, may also be factors.[2]

Weiss[3] has reported in detail the psychic experiences of adult prison inmates following the ingestion of powdered nutmeg. Nutmeg has been mentioned as one of the substances now prominent in illegal or quasi-legal use among adolescents.[4] There are no detailed reports about the use of this substance by adolescents.

Case report

The following is an account of the experiences of an eighteen-year-old student who ingested half a can (one fourth of a teacup) of commercially available nutmeg. His girl friend who was present throughout this experience did not partake of the nutmeg. He had taken marihuana on several occasions before that and had experienced vivid imagery under its influence. About two weeks had elapsed between the last time he had taken marihuana and the time he took nutmeg. The latter substance was taken partly out of curiosity (he had heard about its effect "by the grapevine"), but mainly because marihuana was not then available. Fifteen to twenty minutes after taking nutmeg, a teaspoon at a time and flushing it down with Coca Cola, "things went funny." He felt "as if he had stayed awake for two days without sleeping" and "things started to look unreal" to him. His head shook back and forth, and when somebody said something to him, he could not see the connections between the sentences. He said he remembered that he "spoke up and nobody understood him" either.

About one and a half hours after the ingestion, he started feeling "as though he had drunk fifty cups of coffee." He "could not stop shaking," he "was "giggling," he "was saying stupid things," things he would not have said otherwise. His friend became aware of the change in him. The patient remembered she asked him whether or not he felt all right. "Peoples' voices appeared to come out of a porthole above my head." He "felt a tingling" in his hands, and presently his "whole body felt numb." Friends laid him down on the floor, and he remained there for some time. Finally he opened his eyes, looked at the lights on the ceiling, and felt they were cylinder-shaped. He raised his hands, grabbed one of those cylinder light beams, and sat up, "pulling himself up by that beam." He was still aware of his surroundings and noticed that people were watching him. His heart was beating fast, he was breathing hard, and his throat felt dry. Fortunately, he was constantly accompanied by his friend who subsequently corroborated his recollections. He "felt as though he was floating" but "he knew that in reality he was not floating." He knew that "friends were helping" him. His "legs felt numb" and as if "he was walking in a lake with the water up to his waist." His "hands appeared white and wrinkled" to him.

At that point, he started feeling as if he was in a trance, and it was the first time that he did not know that people were around him. As he gradually came

out of the trance, he could feel a ball in his hands; this ball would expand and contract as he moved his hands, but he could not see the ball. His friend said, "Touch something real!" He then touched the table and felt real again.

Subsequently, he felt he kept going in and out of a trancelike state and could, on several occasions, even induce it himself. As he was walking, he felt that the floor was bow-shaped, and he had to hold on to the wall.

He recalled that the following three hours were accompanied by these experiences: He would sit on a couch and he would drift away completely, "a great fog would be closing in" on him, and when he was surrounded by this fog "everything would turn black." "Spots of color, blue and red, would shine through this black cloud." Beyond the cloud, there seemed to him to be infinity. He "heard a massive confusion of sound," although to his knowledge there was no one talking and there were no sounds of any other nature at that time. But, again, when his friend called his name, he "came out of it." At times he felt excited, at times he felt relaxed. He remembered that he would often ask his friend to talk to him to keep him in reality. He found that he could, in this way, practically control his state of mind; that is, whether he would be in a trance state or not.

When he looked at the picture of a countryside with deer in it, he felt as though he were floating into the picture and it took on a three-dimensional character. The deer were alive, the trees had shape. He started feeling everybody in the world could hear him. When he went out of the house and stepped onto the lawn, he anticipated that he would fall into it, as if into an ocean. He started writing in mirror writing, "Help! I'm trapped behind the world."

He played a few notes on his recorder and felt that "each note was a brown disc." He then played a record; "the sound of music made a pattern of color. There was a central color and lines around it. The center was composed of the low notes, the bass, and the high notes were on the periphery." He remembered that sounds made by "cymbals were silvery." This configuration kept changing, beating, and throbbing. Finally, he could stand it no longer, and he turned the music off.

By this time, some eight or nine hours had elapsed from the ingestion of nutmeg. He started becoming confused, and memory (recall) became very poor. He fell asleep and seemed to realize that he could finally go to sleep without "dropping out."

Comment

The preceding narrative was given spontaneously by an intelligent, perceptive, and sensitive adolescent who had had prior experience with marihuana and morning-glory seeds. The frequent connection of the two is known.[2,5] He felt that on marihuana, the predominant feeling was one of enjoyment and happiness, of being liked and floating. Hallucinations were less marked. On morning-glory seeds, he also had a light, floating sensation, but it seemed to be of a different kind, and the most marked thing was a constant feeling of euphoria. On both these substances, he felt he never really left reality, and he thought that this was a major distinction between these substances and nutmeg.

He repeated his experience with nutmeg in a smaller dose. On one tablespoon full of the substance he "felt high" or sometimes "weird," but without hallucinations; music sounded better although it did not sound louder. None of the colorful changes in perception occurred on the small dose of nutmeg.

The description given by this patient is richer and more colorful than the previous reports,[2,6,7] although the previous descriptions also contained many of the experiences reported here, such as lapses of attention, although consciousness was retained,[6] depersonalization,[6] bright colors,[7] a floating feeling,[2] and music being more enjoyable.[2]

Follow-up on this patient showed that he continued taking marihuana but stopped taking nutmeg. Psychodynamically, the patient was in the midst of an identity crisis, trying to deal with his leanings toward dependency and passivity by identifying with the "hippie" groups. The pa-

tient's father had been incapacitated for several years because of psychiatric difficulties also centering around dependency and passivity.

Summary

Some of the pertinent literature on the use of nutmeg as a hallucinogen is briefly reviewed. It is noted that descriptions of experience with this substance in adolescents are lacking.

Feelings of depersonalization and unreality, changes in perception, as well as illusions and hallucinations, especially visual, were the significant aspects of the subjective experience of an eighteen-year-old adolescent. The patient was also able to differentiate the effects of nutmeg from those of marihuana and morning-glory seeds, on the basis of a temporary break with reality which he experienced with nutmeg.

Although the unfortunate easy availability of other hallucinogens probably makes nutmeg intoxication a relatively rare occurrence, mainly as experimentation or when other substances are not available, the medical profession should be reminded of its possible use and its hallucinogenic effects.

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Death rate in firsf half of year

The death rate from all causes among Metropolitan Life Insurance Company's standard ordinary policyholders was the same in the first half of 1968, 617.1 per 100,000, as in the corresponding period of 1967.

Mortality rates from each of the major causes were lower than last year, except for pneumonia and influenza, cancer of the respiratory system, accidents, and war deaths. The largest increase in death rates by cause, 9 per cent, was from pneumonia and influenza, reflecting the epidemic of respiratory infections earlier in the year.

The motor vehicle death rate rose 7 per cent. In contrast, diabetes mortality rates declined 9 per cent, and suicides were down 8 per cent. The death rate from cardiovascular-renal diseases as a group, which are responsible for over half the deaths among these policyholders, recorded a slight decline. The death rate from cancer, all forms, declined 3 per cent, even though the mortality rate from respiratory cancer increased somewhat over that of a year ago.

Br. J. Addict, 1968, Vol. 63, pp. 105–109. Pergamon Press. Printed in Great Britain.

Nutmeg as a Psychoactive Agent

R. T. BEATTIE, M.A. (Cantab.), M.A.*

There is an increasing volume of casual evidence that the ordinary domestic spice nutmeg (the seed of *Myristica fragrans*) is being consumed in some circles for its supposed psychological effects.[1] Nutmeg-taking seems to be more common in the United States where it is popular with students, with other groups in which drugs are taken for pleasure purposes and with prisoners.[2] The effects reported are diverse; in the main, users claim that nutmeg causes arousal or elation, and some report merely that it makes them "high" or gives them a "lift". Students have suggested that nutmeg makes questions look easy and also that sometimes it causes very unpleasant reactions.

Weil emphasizes that the expectations of the user play a large part in determining the experience of drug-takers which may account for the variety of results said to ensue from consumption of nutmeg. Since there seems to be some uncertainty as to whether nutmeg has any psychological effect, it seemed that a controlled trial using a group of young people might be timely, especially since nutmeg-taking is as yet unpractised here to the same extent as in America.

The null hypotheses set up for investigation were, that after taking nutmeg

(i) formal problems and problem-solving would not seem easier
(ii) no effect on speed or accuracy of problem-solving would occur
(iii) no unusual changes in experience would occur.

An additional hypothesis was that heightened suggestion would increase the reported effects.

METHOD

The subjects were 42 first-year psychology students divided into drug and placebo sections. Within each section some were subject to low-suggestion preparation and some to high-suggestion, making four groups or conditions in all. Each group was dealt with as a body and the experiment took 2½ days to complete; the low suggestion groups were seen in the first 24 hr and were asked not to discuss the experiment with other groups. It was expected that some leakage of information would occur and that this would heighten the suggestion given to the remaining two groups which were both dealt with on a later afternoon.

The procedure was that each group assembled and was told that they would be concerned with testing the effects of a substance on behaviour and problem-solving. In order to increase the general credibility of the situation it was stressed that only volunteers should participate. The volunteers then entered the laboratory and took their places, and at this stage the low suggestion placebo (LSP) and low suggestion drug (LSN) groups were prepared by statements to the effect that the *possible effects* of the *substance* should be recorded in the manner indicated. High-suggestion groups (HSP and HSN) were told to record the *effects* of the *drug*, that the

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Hypothesis (iii)

Very few subjects wrote anything at all about subjective experiences on their problem answer sheets. When presented with the check list afterwards the mean numbers of statements underlined were:

Drug groups, 4·7 Placebo groups, 3·0.

A test of the difference between these means yields a value of t of 1·81 which is not significant.

The drug does not increase the number of statements made beyond that of the placebo group.

However, the members of the drug group were more varied in the numbers of statements underlined by individuals.

Variance of drug groups = 12·19. Variance of placebo group = 4·70

Ratio = 2·59 ($p < 0·05$).

Hypothesis (iv)

From the check lists the mean number of items underlined
for combined LS groups was 4·2 ($N = 26$)
and for combined HS groups was 3·6 ($N = 16$).

Clearly, the attempt to heighten suggestion in the HS groups did not increase the reported effects and the hypothesis must be rejected.

DISCUSSION

It seems that nutmeg, taken in this quantity, has no greater effect than a placebo. The only difference, a not very significant one, was that the members of the drug groups were more varied as individuals in the number of statements which they underlined. This could mean that nutmeg was having a slight effect in that certain statements, reflecting the subjective changes due to the drug, were being substituted for and added to those statements underlined by reason of suggestion alone. In other words, there might have been qualitative rather than quantitative changes.

If this were so it could reasonably be expected that the drug groups would tend to mark statements in a different but overlapping set of categories to the placebo groups. The frequency with which the eight categories were employed by the two groups are contrasted in Table 1; the value of χ^2 attained is 8·5 which is not significant.

TABLE 1. FREQUENCIES OF RESPONSE BY DRUG AND PLACEBO GROUPS TO THE EIGHT CATEGORIES OF SUBJECTIVE CHANGE

	(i)	(ii)	(iii)	(iv)	(v)	(vi)	(vii)	(viii)
Placebo	20	7	5	3	8	2	19	3
Drug	27	11	13	9	11	9	16	3

It appears to be the case that, in all groups, suggestion has determined the outcome. The greater variance of the drug groups may therefore be attributed to the more varied susceptibility to suggestion of their individual members.

Some difficulties arise over the amount of nutmeg customarily taken, for the quantity varies from one account to another. The amount given in this experiment is in accord with most oral reports and probably exceeds that employed by those who prefer to smoke nutmeg mixed with tobacco. In four cases known to the author, in which from ten to twenty times the amount used here was taken, the results were in no way different to those obtained from these subjects. If nutmeg has any effect at all, some changes should have occurred in these subjects and should have been reflected in either the check list or the two opportunities given for free reporting or in performance on hard formal problem-solving.

The procedures for heightening suggestion do not seem to have been effective. In fact the necessary preliminary operations common to all groups seem to have maximised the effects of suggestion on this occasion. The outcome of asking for volunteers (in each group three people left at this stage) was so suggestive in itself that further verbal "information" or lack of it had no effect. It is perhaps worth emphazising this observation because it indicates that in this case the most brief, neutral statements about the substance were sufficient to induce the illusion of real changes. It is perhaps not necessary that suggestion should be heavily played when credibility is high.

Enquiries at a later date indicated that the credibility of the situation was considerable. Most subjects appeared to have lost all critical ability since very few suspected that placebo groups might be included in the experimental design and all of them consumed the substances in a serious-minded way. Some were certain that they had been given tranquilizers or LSD.25 or even heroin, when a moment's reflection would have shown them that the consequences of such action on the part of the experimenter would have been disastrous and thus highly unlikely.

CONCLUSION

Nutmeg has no psychological effect in the areas of behaviour sampled when given in this quantity. It seems highly unlikely that it has any effect when given in larger amounts, and it therefore seems most probable that reports of its effectiveness are based entirely upon subjective experiences induced by the suggestiveness of the conditions under which it is taken.

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Résumé—La muscade n'a pas d'effet psychologique dans le domaine du comportement, quand elle est administrée dans cette quantité. Il paraît très improbable qu'elle ait quelque effet quand elle est donné dans des quantités plus grandes; donc, il paraît très probable que les rapports publiés concernant son efficacité sont basés sur des expériences subjectives causées par la signification des conditions dans lesquelles elle a été prise.

Zusammenfassung—Muskatnuss, wenn in diesen Mengen verabreicht, hat keinerlei psychologischen Effekt im Bereiche der Verhaltens-Erhebungsauswahl. Auch scheint es höchst unwahrscheinlich, dass bei Verabreichung grösserer Mengen eine Wirkung erzielt wird, weshalb es sehr wahrscheinlich ist, dass sich Berichte über die Wirksamkeit dieses Mittles vollständig auf subjektive Erfahrungen stützen, welche durch Beziehungsandeutungen der Bedingungen, unter welchen es eingenommen wurde, ausgelöst wurden.

These observations suggest the possibility of dividing the *Mycoplasma* into 3 groups according to their effect on mammalian cells growing in tissue culture. The rather general working classification outlined below may prove useful and convenient in distinguishing saprophytic from pathogenic PPLO. Perhaps the first large division might include saprophytic Mycoplasma such as *M. laidlawii* which shows little if any growth or multiplication in tissue cultures. PPLO considered to be primarily endogenous tissue culture contaminants, in that they persist in small numbers and establish an ecological equilibrium with the host, may comprise another large group. The third division could be composed of those PPLO thought to be potentially pathogenic for cell lines when maintained 2 to 3 weeks in tissue culture, particularly when PPLO metabolic processes supplement or alter host cell metabolism. The reported data suggest that the strain of *M. gallisepticum* studied, when growing in FL cells is a rather typical agent according to the third suggested PPLO grouping.

Summary. Infection of FL tissue culture cells with *M. gallisepticum, M. agalactiae* and *M. hominis* was achieved, while the saprophytic PPLO *M. laidlawii* A could not be detected in such cells when cultivated for intervals longer than 2 days following infection. Parasitic PPLO remained in cell cultures for periods up to 3 weeks. After prolonged incubation, cytopathogenic effect could be demonstrated in cultures infected with *M. gallisepticum.* In addition, tissue cultures infected with *M. gallisepticum* showed an accumulation of acetate in growth fluids. The latter observation, supported by appropriate isotope data, strongly suggests that acetate appears as a product of lactate dissimilation by this PPLO.

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Evidence of Monoamine Oxidase Inhibition by Myristicin and Nutmeg. (28128)

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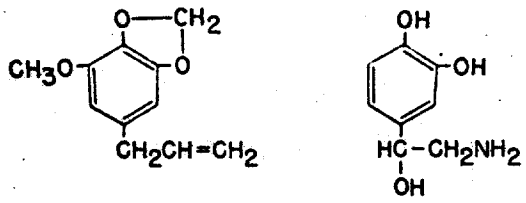
Nutmeg, the seed of *Myristica fragrans,* contains a terpene-like compound, myristicin, which for years has been identified as the principal active ingredient. This early observation of Sir Henry Dale has been recently confirmed using both animal and human tests (1). Nutmeg intoxication produces an unusual syndrome in man involving, first, stimulation and a feeling of euphoria. This may extend into an acute toxic psychosis with an overdose and may be followed by a depressed state during recovery.

There is a degree of structural resemblance between the chemical formula for myristicin and those of certain sympathomimetic amines. This is especially true when the methylenic group of myristicin is considered as isosteric with an amino group. This analogy is shown in Fig. 1. This similarity coupled with the stimulating action of nutmeg prompted a preliminary evaluation of myristicin and crude ground nutmeg for evidence of central monoamine oxidase inhibition.

Materials and methods. Ground East In-



Myristicin Norepinephrine

FIG. 1

dian Nutmeg from a single large batch was given orally in 2% acacia suspension. Chemically synthesized myristicin was dissolved in liquid petrolatum for oral or intraperitoneal administration. A distilled concentrate of oil of nutmeg containing representative amounts of the volatile components was given orally without dilution. Tranylcypromine and iproniazid given orally served as comparative standards.

The method of Tedeschi *et al.*(2) for estimation of monoamine oxidase (MAO) inhibition by measurement of potentiation of tryptamine convulsions was modified and applied to mice. Graded doses of tryptamine HCl 0.5% solution were injected intravenously into 10 mice per dose level. Three seconds or more of clonic jerking, tremors and/or side-to-side head movements were the endpoint criteria used to calculate the CD_{50} from dose-response lines by the method of Litchfield and Wilcoxon(3). Palpebral ptosis was estimated by the method of Rubin *et al.*(6) in rats scoring both eyes on a 5 point scale. Cerebral 5-hydroxytryptamine was measured by the Mead and Finger modification(4) of the method of Bogdanski *et al.*(5).

TABLE I. Tryptamine Convulsion Test for Monoamine Oxidase Inhibition *in vivo*. Summary of control tests.

Species	No.	Vehicle–18 hr prior, cc/kg	CD_{50}, mg/kg	95% confidence limits, mg/kg
Mouse	40	None	25.0	15.4-40.5
"	21	"	17.3	12.1-24.7
"	28	Liq. pet.	24.5	19.9-30.1
"	38	" "	28.0	18.4-42.6
"	37	Acacia–2%	25.8	18.3-36.3
Avg	164		25.0	21.6-29.0
Rat	54	None	18.6	13.6-25.5

Results. No apparent effect was evident from the drug vehicles on the CD_{50} of tryptamine (Table I). When given orally 18 hours in advance, East Indian ground nutmeg gave some evidence of tryptamine potentiation (Fig. 2). The optimum dose was 500 mg/kg. However, a much larger dose, 1000 mg/kg, showed reversal of the activity.

Several samples of synthetic myristicin were tested by the tryptamine potentiation test 18 hours after their oral administration. These results are shown in Fig. 3. Both of these preparations showed considerable activity when the sample was fresh and lemon yellow in color. Later tests (not shown) after the liquid had turned to a light amber color consistently showed a considerable decline in tryptamine potentiation. These deteriorated solutions when studied by gas chromatography showed the appearance of an additional component to the myristicin of unknown identity.

The distilled concentrate of oil of nutmeg was much less active than the synthetic myristicin and, like ground nutmeg, reversed its activity with a large dose (Fig. 3). Gas chromatographic analysis of this oil showed the presence of similar volatile components to ground nutmeg, but no increased concentration of the myristicin as expected from the selected distillation temperature.

In Fig. 4 the slope and activity of the best tryptamine assay for myristicin is compared to tranylcypromine and iproniazid. All 3 drugs were administered orally 18 hours before the test. It may be seen that myristicin is less potent but parallel to the comparative drugs. Safrole, isoborneol and geraniol, which are other volatile components of nutmeg, did not cause potentiation of tryptamine in doses up to 1 g/kg despite obvious signs of hyperactivity and excitement in the mice.

In Fig. 4 the antagonism of reserpine ptosis in rats was used to study variations in dose and time for myristicin activity. Myristicin appears to be less active in the rat. Comparable activity to other MAO inhibitors was obtained only with the largest dose 17 hours after oral administration.

Myristicin treatment of 6 rats increased

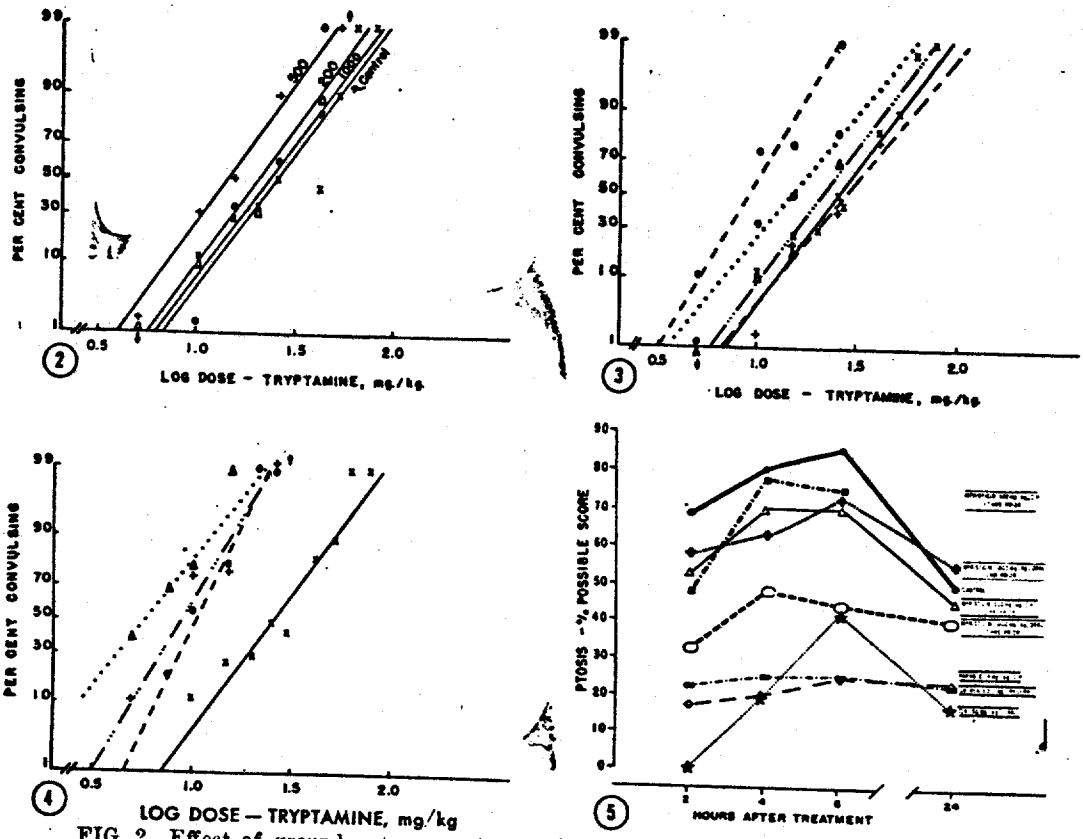


FIG. 2. Effect of ground nutmeg on tryptamine convulsive threshold in mice when given orally in acacia suspension 18 hr before test. ×———× Control, CD_{50} mg/kg (± 95% confidence limits) 25.0 (15.2-41.0); ○—200—○ 200 mg/kg nutmeg, 20.0 (14.2-28.2); +—500—+ 500 mg/kg nutmeg, 14.0 (10.1-19.5); △—1000—△ 1000 mg/kg nutmeg, 23.0 (16.1-32.9).

FIG. 3. Effect of synthetic myristicin samples and oil of nutmeg concentrate on tryptamine convulsive threshold in mice when given orally in acacia suspension 18 hr before test. ×———× Control, CD_{50} mg/kg (± 95% confidence limits) 25.0 (15.2-41.0); ●— —● myristicin sample 1 at 500 mg/kg, 8.7 (5.7-13.4); ○—···○ myristicin sample 2 at 500 mg/kg, 14.0 (9.3-21.0); · · · · · oil of nutmeg concentrate 500 mg/kg, 20.5 (14.5-28.9); +——— —+ oil of nutmeg concentrate – 1000 mg/kg, 27.0 (19.9-36.7).

FIG. 4. Effect of monoamine oxidase inhibitors and synthetic myristicin on tryptamine convulsive thresholds in mice when given orally in acacia suspension 18 hr before test. ×———× Control, CD_{50} mg/kg (± 95% confidence limits) 25.0 (15.2-41.0); ○— —○ 150 mg/kg iproniazid, 10.4 (8.8-12.2); △ · · · · △ 4 mg/kg tranylcypromine, 5.8 (4.4-7.7); +—···+ 500 mg/kg, 8.7 (5.7-13.4).

FIG. 5. Effect of monoamine oxidase inhibitors and various schedules of myristicin on reserpine ptosis in rats. Ptosis score: 0 = Eyelid fully open — 5 = Eyelid fully closed. Maximum score = 10/rat (both eyes). Group ptosis score (%) $= \frac{\text{No. rats/group} \times \text{Max score/rat}}{\text{Sum of group eyelid scores}} \times 100$.

brain 5-hydroxytryptamine from control values averaging 0.48 (± 0.05) μg/g to 0.82 (± 0.03) μg/g when given in an oral dose of 1 g/kg and the difference was statistically significant ($p<0.001$). Lower doses were not significantly active.

Discussion. These data may be taken as preliminary evidence of MAO inhibition by nutmeg and myristicin. Further corroboration is necessary by tests of brain MAO kinetics *in vivo* since aqueous solution of myristicin is impractical. These studies are in preparation.

Although the evidence of MAO inhibition through an effect on tryptamine is indirect, Maxwell *et al.*(7) found very good correlation between tryptamine toxicity in mice and *in vivo* MAO inhibition in mouse brain. Res-

erpine antagonism is a general characteristic of both MAO inhibiting and iminodibenzyl types of anti-depressant drugs. The ability of myristicin to increase brain 5-hydroxytryptamine is also circumstantial evidence for enzyme inhibition.

Even though they are not markedly potent inhibitors of MAO, nutmeg and myristicin are relatively safe compounds with respect to human toxicity. Doses of 10-15 g are required to produce acute intoxication in man with ground nutmeg. Oral doses in amounts up to 400 mg of the distilled concentrate of oil of nutmeg have not shown toxicity in human volunteers(1).

A preliminary human trial with nutmeg has been carried out in one depressed and 4 schizophrenic patients by Dr. Albert A. Kurland at Spring Grove State Hospital. Capsules of ground nutmeg containing 500 mg were given 3 times daily for 3 weeks. One patient was markedly improved, 3 showed some improvement and 1 showed no response. A further trial is contemplated in patients showing more depressive symptoms as a part of their mental difficulties.

The instability of synthetic myristicin appears to be a problem in its evaluation and use as the active component of nutmeg. Gas chromatographic evidence showing formation of an additional peak in aged preparations confirm this possibility. However, no precautions other than cold and the exclusion of light were taken with the synthetic compounds.

Summary. Nutmeg and its active component, myristicin, show evidence of central monoamine oxidase (MAO) inhibition by their ability to lower the convulsive dose of intravenous tryptamine in mice and to increase rat brain 5-hydroxytryptamine concentrations. They also show some ability to antagonize reserpine-induced ptosis of the eyelids. Myristicin is chemically unique as a nitrogen-free MAO inhibitor. Although its potency in this respect is not comparable to some of the more potent inhibitors such as tranylcypromine and iproniazid, it seems quite adequate when compared to its low toxicity. Other volatile components of nutmeg such as borneol, geraniol and safrole, do not show tryptamine potentiation, although some appear to cause C.N.S. stimulation in high doses. Further study is recommended for more direct evidence of nutmeg and myristicin as enzyme inhibitors and for their utility as anti-depressant drugs.

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31a

OILS OF MYRISTICA

Oil of Nutmeg and Oil of Mace

Essence de Muscade and *Essence de Macis*
Aceite Esencial Nuez Moscada and *Aceite Esencial Macis*
Muskat- and *Macisöl* *Oleum Nucis Moschati* and *Oleum Macidis*

Introduction and History.—Nutmeg (myristica) and mace are both derived from the fruit of *Myristica fragrans* Houtt. (fam. *Myristicaceae*), nutmeg being the dried ripe seed, and mace the dried arillode which envelops the shell containing the seed or nutmeg. Both are very important spices, which have been used for a long time in the flavoring of savory dishes, baked goods, and other food products. They owe their characteristic aroma chiefly to the presence of an essential oil which can be isolated by steam distillation. Oil of nutmeg and oil of mace are very similar in odor and flavor, and since the nutmeg suitable for distillation is usually lower priced than mace, the former is generally employed for commercial production of the volatile oil.

According to some authors, nutmeg and mace—the latter particularly—were highly valued by the ancient Romans, who sometimes used them as a form of currency. According to other, and more reliable, sources, however, nutmeg was unknown to the Romans, becoming familiar in Europe only during the twelfth century, after it had been introduced from the East perhaps by returning Crusaders or by Arabian physicians.[1] In 1158 *"Nuces muscatarum"* imported from Alexandria were traded in the harbor of Genoa.[2] The true origin of the spice was discovered only at the beginning of the sixteenth century (in 1512) by two travelers, Barthema and Pigafetta.[3] At that time the Portuguese conquered the Moluccas, those fabled spice islands, and declared the trade in nutmeg and mace a monopoly. In 1605 the Hollanders drove the Portuguese out of the Moluccas and, taking over the spice monopoly, restricted the production of nutmeg and mace to Banda, and that of clove to Amboyna, in order to keep up prices. The monopoly of the Hollanders lasted for almost two hundred years. In 1769 the French succeeded in introducing the nutmeg tree to Ile

[1] Cf. "Nutmeg and Mace.—A Note on Their History," *Perfumery Essential Oil Record* 7 (1916), 76. Cf. *Ber. Schimmel & Co.* (1912/13), 26.
[2] Cf. Gildemeister and Hoffmann, "Die Ätherischen Öle," 3d Ed., Vol. I, 131.
[3] G. B. Ramusio, "Delle Navigationi et Viaggi," Venice (1551), fol. 183 and fol. 389b.

de France (now Mauritius), east of Madagascar; in 1796 Christopher Smith collected spice bearing plants in the Moluccas for the powerful East India Company. These were brought to Penang, where the first commercial crop of nutmeg and mace was gathered about 1802. This marked the end of the Dutch monopoly (which included cloves; in fact, the history of the clove trade almost parallels that of the commerce in nutmeg and mace). Early in the nineteenth century, numerous nutmeg plantations were started in many parts of Malaya and the Indonesian Archipelago, and about 1813 the tree was introduced also to Grenada in the West Indies, a small island which today produces about 40 per cent of the world's output of nutmeg and mace.

Producing Regions and Qualities.—The trade recognizes today two principal types of nutmeg (and mace), the difference between the two being based not only upon geographical origin, but also upon quality of the spice:

(1) *East Indian Nutmeg and Mace.*—According to Nijholt,[4] *Myristica fragrans* Houtt., which yields the so-called "Banda Nutmeg," is grown extensively in Indonesia, chief producing areas being the Moluccas, Minahassa (northern Celebes) and the Sangih Islands, Benkulen (West Sumatra) and Achin (North Sumatra), including the island of Nias. Throughout Indonesia nutmeg plantings are owned by natives, or occasionally by Chinese.

According to Landes,[5] there are four grades of East Indian nutmegs:

(a) The "Banda Nutmegs," considered perhaps the finest for commercial use, and containing about 8 per cent of essential oil.

(b) The "Siauw Nutmegs," considered almost as good as the "Banda," but containing only about 6.5 per cent of essential oil.

(c) The "Penang Nutmegs." Prior to World War II, these were of good quality; but they are now wormy and moldy beyond the possibility of reconditioning, probably as a result of neglecting plantations during the war, and can be used only for distillation purposes.

(d) The "Papua Nutmegs." These are among those nutmegs not derived from *Myristica fragrans* Houtt., but from an allied species, viz., *Myristica argentea* Warb. They can easily be recognized by their shape and peculiar, unpleasant odor. Papua nutmegs have been imported into the United States only since the last war. They should not be used for distillation, the yield of oil being low, and the oil possessing an odor reminiscent of sassafras.

In addition to the four above-mentioned grades, there is, perhaps, a fifth

[4] Private communication from Dr. J. A. Nijholt, Director of the Laboratorium voor Scheikundig Onderzoek, Buitenzorg, Java.

[5] Private communication from Dr. Karl H. Landes, New York.

grade, the so-called "Java Estate Nutmegs," small quantities of which enter the United States market. They are of very good quality and may be classified as an intermediate between the "Banda" and the "Siauw" nutmegs.

As was pointed out above, the "Papua" nutmegs are derived from a species of *Myristica* other than *fragrans* Houtt. Whether this is the case also with some of the other grades lower than the "Banda" cannot easily be ascertained. *Myristica succedanea* Bl., in Indonesia called "Pala Maba," e.g., produces a grade of nutmeg and mace which is only slightly, if at all, inferior to the first grade "Banda" spice. (The oils derived from species of *Myristica* other than *fragrans* Houtt. will be described in separate monographs. The present monograph will deal exclusively with the oils of nutmeg and mace from *Myristica fragrans*, both East Indian and West Indian.)

As regards the grades of mace produced in East India, Landes[6] distinguishes between the following:

(a) The "Banda Mace," considered the finest. This is prepared for the market with more care than any other grade of mace, being artificially dried and fumigated in specially constructed dryers and carefully sifted. Any broken pieces are eliminated. The color is bright orange, the aroma very fine.

(b) The "Java Estate Mace," grown near Semarang, in Java. Like the "Banda," this is artificially dried, and quite free of insect infestation. It can easily be recognized by its round shape and its gold-yellow color, interspersed with brilliant crimson streaks.

(c) The "Siauw Mace," originating from the islands of Celebes, Ternati, Talanda, and Sangi. The color is lighter than that of the "Banda"; the brighter the color, the higher the price. Depending upon color and size, the Siauw mace is classified as of No. 1 and No. 2 quality. Broken pieces are classified as siftings. In general, Siauw mace contains about 10 per cent less volatile oil than the Banda mace.

(d) The "Papua Mace," derived from *Myristica argentea* Warb. This type is entirely unsuitable for the purposes of grinding or distilling, since it contains a high percentage of fatty oil and comparatively little essential oil. (The latter exhibits an undesirable turpentine-like aroma.)

The above-mentioned grades of East Indian mace contain, on the average, the following quantities of volatile oil:

	Per Cent
"Banda Mace"	13
"Java Estate Mace"	11 to 12
"Siauw Mace"	10 to 11
"Papua Mace"	4

[6] *Ibid.*

West Indian mace (which will be described below) yields from 8 to 9 per cent of essential oil.

Nijholt [7] reported the following figures for nutmeg and mace exports from Indonesia in the years 1936 to 1940 inclusive, and 1948, in metric tons:

	Nutmeg	*Mace*
1936	4,192	777
1937	4,415	823
1938	3,977	834
1939	4,215	810
1940	3,612	847
1948	2,676	494

Shelled nutmegs are usually shipped directly from the harbors near the producing regions to the consuming countries. Singapore does not handle much of this type. However, of the unshelled nutmegs, about 75 per cent of those produced first go to Singapore for transshipment abroad.

In 1938 a total of 435,867 kg. of nutmegs ("distillers grade") was exported from Macassar (Banda). These exports were distributed as follows: [8]

	Kilograms
United States	389,451
Holland	15,345
Holland, Option	6,131
Great Britain	11,528
Great Britain, Option	5,120
Germany	8,292
	435,867

According to Swing,[9] the nutmeg tree was introduced to Ceylon in 1801, and now grows on the island in deep loamy soil, up to an elevation of 2,500 ft. In 1946 Ceylon exported 1,063 hundredweights of nutmeg, in 1947 the exports amounted to 1,488 hundredweights.

(2) *West Indian Nutmeg and Mace.*—Until 1939 the West Indies produced only about one-sixth of the world's supply of nutmeg and mace, but since the outbreak of World War II (when the spice from the East Indies became unavailable) production in the West Indies has increased to about 40 per cent of the world's output. The bulk of the West Indian nutmeg and mace originates from the small British island of Grenada, one of the Windward Islands, lying just to the north of Trinidad. Before World War

[7] Private communication from Dr. J. A. Nijholt, Director of the Laboratorium voor Scheikundig Onderzoek, Buitenzorg, Java.
[8] *Ber. Schimmel & Co.* (1939), 53.
[9] *Spice Mill* 72, No. 2 (1949), 48.

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Grenada's nutmegs and ma...
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Year	*t*
Nutmegs	
1940	2
1941	1
1942	1
1943	2
1944	2
1945	2
Mace	
1940	
1941	
1942	
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1945	

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II the West Indian spice was shipped largely to Great Britain and continental Europe, but during the war the picture changed and the United States became the principal buyer of the West Indian nutmeg.

According to Whitaker,[10] the nutmeg tree was introduced into Grenada about 1843, when the captain of a visiting Dutch ship gave one of Grenada's planters a few of the many nutmeg seeds he was bringing to the Netherlands from the island of Banda in Indonesia. These seeds produced tall, sturdy trees, which flourished in the soil and climate of Grenada. They formed the core of a new industry, which in later years came to provide employment for half of the island's population. As practically all of Grenada's nutmegs and mace are exported, the following table of exports for the years 1940 to 1945 may also be considered as production or crop figures:

Year	*Total (in tons)*	*United Kingdom (in tons)*	*Canada (in tons)*	*United States (in tons)*	*Other (in tons)*
Nutmegs					
1940	2,095	523	128	1,331	113
1941	1,910	700	144	1,015	51
1942	1,876	780	102	921	73
1943	2,270	351	80	1,636	203
1944	2,574	224	110	1,935	305
1945	2,341	500	73	1,553	215
Mace					
1940	274	222	31	20	1
1941	324	302	18	3	1
1942	340	288	10	34	8
1943	334	71	14	223	26
1944	338	41	22	233	42
1945	338	92	24	158	64

According to Landes,[11] the quality of the West Indian nutmegs has been gradually but steadily improving. Shipments now usually meet standards, and lots are rarely rejected because of worminess or an excessive amount of moisture. Recent shipments of West Indian nutmegs have shown a content of volatile oil as high as 9 per cent, which is greater than that of Banda nutmegs from Indonesia. The reason may lie in the fact that many of the nutmeg trees of Grenada have now reached an age of thirty to thirty-five years, i.e., the prime of their productivity.

As regards West Indian mace, its quality is still below that of the East Indian spice, and only the price difference between the two products has

[10] *U. S. Dept. Commerce, Foreign Commerce Weekly*, Washington, D. C., 25 (November 23, 1946), 8.

[11] Private communication from Dr. Karl H. Landes, New York.

compelled some of the grinders to substitute the West Indian for the East Indian mace. The former possesses a nice yellow color, but its texture is brittle, and its volatile oil content (8 to 9 per cent) below that of the East Indian mace. Moreover, the volatile oil exhibits a turpentine-like aroma.

Botany.—*Myristica fragrans* Houtt., one of about 100 known *Myristica* species,[12] is a bushy tree with numerous spreading branches; it attains a height of 30 to 40 ft., in some cases even 60 ft. In its general appearance the nutmeg tree resembles an orange tree. According to Ridley,[13] the trees are in most cases unisexual, bearing male flowers or female flowers only, but it is not uncommon to find a tree with flowers of both sexes upon it. It has long been known that a male tree after some years, usually about six, frequently commences to produce female flowers, and eventually becomes wholly female. The fruit appears on the tree mingled with flowers; in other words the nutmeg tree, like the lime tree, bears flowers and fruit at the same time. The orange-yellow, smooth fruit, when ripe, is one of the most beautiful in nature. A pendulous, fleshy drupe of quite variable form, it is globular on some trees, oval or pear-shaped on others. The size varies, but averages 2.5 in. In general, the fruit resembles a small peach. The husk (pericarp) is of fleshy, somewhat firm texture, and about 0.5 in. thick. It contains an acid, astringent juice with an aromatic flavor of nutmeg. When ripe, the fleshy husk opens by splitting into two halves, from the top nearly to the base, along the groove which runs down one side. On splitting of the husk, the nut appears. It has a deep brown, glossy seed coat or shell that contains the seed. The latter, when dried, is the nutmeg of commerce. The seed coat is partly covered by a peculiar, net-like and crimson, leathery arillode, growing from the base of the seed. The dried arillode is the mace of commerce.

The shell (*testa*) has a woody and brittle consistency; when dried it can easily be cracked to remove the seed (after the arillode has been peeled off the shell by hand). Within the shell a sound seed should measure about 1 in. in diameter. When fresh, the oval seed nearly fills the shell, but on drying, the seed (nutmeg) shrinks somewhat and then rattles within the shell. Seed used for sowing should not be dry enough to rattle, but for trade purposes the nutmegs should rattle in the shell when shaken. A dried, sound nutmeg, removed from the shell, is hard and woody in texture, ovoid or ellipsoidal in form, from 20 to 30 mm. in length and about 20 mm. in thickness, light brown to dark brown in color, reticulately furrowed. When cut, the inside shows a waxy and oily luster, with brown spots on a

[12] There are, however, a few others, the nuts of which are slightly aromatic, and occasionally collected by natives and exported to Europe, more as adulterants of true nutmeg rather than for separate use.

[13] "Spices," London, Macmillan & Company, Ltd. (1912), 94.

grayish ground. The dried seed (nutmeg) contains from 5 to 15 per cent of volatile oil, from 25 to 40 per cent of fixed oil, and from 5 to 15 per cent of ashes; the balance consists of moisture, fiber, and starch.

Mace (the arillode enlacing the shell of the seed), when freshly removed, exhibits a bright red color which, however, changes to orange-yellow on drying. It is marketed in the form of irregularly shaped pieces which swell when immersed in water. Odor and flavor are similar to, yet distinctly different from those of nutmeg. Mace contains from 4 to 14 per cent of a volatile oil closely resembling that derived from nutmegs. West Indian mace has a paler color than the East Indian and is less aromatic.

Production of Nutmeg and Mace in the East Indies.—The nutmeg tree flourishes on a variety of soils, except on bare clay slopes, sandy, or waterlogged soils. The best altitude is from sea level to about 1,000 ft. The tree requires a hot, moist climate and appears to prefer proximity to the sea. Rainfall should be from 80 to 100 in. per year, well spread over the different months, with no absolutely dry spells of more than four to five days, and no continuous rains, without sun, of more than a fortnight. During wet spells parasitic fungi are most active.

According to Ridley,[14] carefully chosen, well-formed seed should be planted within 24 hr. of gathering, if possible, in beds of good soil, well dug over, manured and drained. The seed should be placed from 12 to 18 in. apart in rows, and at a depth of about 2.5 in. The beds need shading under a roof loosely made of leaves, admitting a certain amount of light. The beds should be watered every other day. The seeds require from four to six weeks to germinate, and sometimes longer. The young plants remain in the nursery until they are about 6 in. tall, i.e., for about six months. Then they have to be transplanted, during the rainy season, to their permanent position in the field, at a distance of 26 to 30 ft. apart, either in lines or in quincunx arrangement. The planting holes should be about 4 ft. wide, and at least 3 ft. deep. In hot places the young plants need a certain amount of shading until they have settled in the ground and begun to push out their roots. Being in its natural state a jungle plant, the nutmeg tree grows better and remains healthier when partly shaded (e.g., by the well-known "rain tree" *Pithecolobium saman*), than when fully exposed to the hot sun.

The tree does not flower until the eighth or ninth year, after which it bears flowers and fruit together for many years. The nutmeg tree is normally monoecious, i.e., either male and bearing only male flowers, or female and bearing only female ones. Obviously, only the female flowers produce fruit, but a small proportion of male trees (about one in ten) is required to

[14] *Ibid.*, 107.

provide the pollen necessary to fertilize the flowers on the female trees. Native growers, therefore, usually exterminate most of the male trees as soon as the trees have sufficiently developed to show their flowers and so become distinguishable. This, however, is possible only about seven years after planting. More progressive growers then head down any superfluous male trees and graft them with scions of female plants.

The trees commence to fruit usually in the eighth or ninth year, but reach their prime of productivity only when about twenty-five years old. They bear well up to sixty years, or even longer. The fruits ripen about six months after the flowering period. The fruit is ripe when it splits and shows the shell of the seed enlaced with its brilliant red mace. The fruits are sometimes allowed to drop to the ground; nuts and attached mace are then picked up daily and collected in baskets. The usual practice, in Indonesia, however, is to pull the fruit off the branches by hand, using hooked staffs to reach fruit on lofty branches. A good worker can collect from 1,000 to 1,500 nuts a day.

The yield of nutmeg and mace per tree varies considerably. A healthy tree should average 1,500 to 2,000 nuts per year. As regards weight, each tree should produce 10 lb. of nutmegs to 1 lb. of mace; some trees give much more than this (Ridley).

The tree bears fruit more or less all the year round, but in most places the heaviest crops are obtained in May and June, and again in August and September.

After arrival of the collected material at the working shed the mace (arillode) is detached from the shell of the seed with a knife, or simply by hand, by opening it from the top of the shell and reflexing it. The mace is attached to the seed only by its base, known as the heel of the mace. The freshly removed mace is flattened out by hand, spread on bamboo trays or on mats, and dried in the sun from 4 to 5 hr. a day for a fortnight. During dry weather drying may be accomplished in two or three days. Before nightfall the trays or mats must be brought into a drying-shed, to prevent wetting of the material by dew. Great care must be exercised to prevent the mace from getting moldy, which may easily happen. When fresh, the mace possesses a brilliant red color; on drying this changes to orange, and after a few months to yellow.

According to Ridley,[15] a perfect sample of mace should consist of entire double blades (not broken), flattened and of large size, horny in texture, not too brittle, and of good, clear and bright color.

After removal of the mace the nuts are placed on trays and exposed to the sun for several weeks until dry. Often drying is completed over a slow

[15] *Ibid.*, 146.

charcoal fire in a drying-house, care being exercised not to raise the temperature too high, as the seed will then shrivel and diminish in value. The seeds are dried while still in the shell (the thin, brittle outer coating, or *testa*) because otherwise they are attacked by beetles. Drying is completed when the seed rattles within the shell. When the seeds are sufficiently dry, the shells must be removed; this is usually accomplished by hitting them on the end (not on the side!) with a wooden club or mallet. Machines for cracking of nutmegs have been invented and are used on some of the large estates. Once the seed has been removed from the shell, it is exposed to the attacks of all kinds of beetles, especially while stored in the warehouse ("godown"). The beetles deposit eggs in the seed, and the larvae bore holes into it, destroying part of it. Most of these beetles are pests common in the godowns, attacking all kinds of food products. Therefore, the godowns should be thoroughly cleaned from time to time. To prevent damage by insects, the nutmegs are often limed at the place of production. In some parts of Indonesia this is done by sprinkling the dried nutmegs profusely with powdered lime, or by rubbing each nut individually with the chemical, or by dipping them into a mixture of lime and water. At one time, fumigation with sulfur dioxide was occasionally practiced, but this has now been largely abandoned. A more recent method is fumigation of the nutmegs with methyl bromide, in special chambers. However, at the present time, most of the Indonesian product reaches the world markets untreated.

On arrival at the warehouse, the nutmegs are tested by sounding. This is done simply by bouncing them individually on an iron plate. The assorter can thus detect worm-eaten and damaged specimens, which he removes. Sound nutmegs are assorted according to their size and number per pound. At the time of the author's visit to Malaya and Indonesia, just prior to the outbreak of World War II, nutmegs were classified as follows:

(a) Whole, sound nutmegs. These ranged from 60 to 125 nutmegs per pound, the greatest demand being for 85 to 95 nuts per pound. They were known as "Large" (60 to 80 per lb.), "Medium" (85 to 95 per lb.), and "Small" nutmegs (100 to 125 per lb.), and were sold to the spice trade.

(b) Sound shrivels. A quality much in demand for grinding.

(c) Rejections. Because of their low price, these are suitable for distillation.

(d) Broken and wormy. The quality most suitable for distillation because of the low content of fatty oil. Prior to World War II large quantities were shipped to Europe, particularly to Hamburg. The United States permits entry of this grade only under condition that the material be used exclusively for distillation.

Production of Nutmeg and Mace in the West Indies.—As has been mentioned, the nutmeg tree was introduced to Grenada about 1843, when a

Dutch ship bringing spices from Indonesia to Holland called on this small island in the West Indies.

According to Whitaker,[16] in the Windward Islands the trees appear to grow best at an elevation ranging from 500 to 1,500 ft. above sea level, in areas where the rainfall is fairly constant throughout the year. A large part of the fertile mountain slopes of Grenada above 800 ft. elevation is covered with dense groves of nutmeg trees. These trees grow very close together on the steep hillsides, forming an almost unbroken canopy above the ground. The hillsides slope so sharply that mechanical cultivation cannot be practiced; hence the trees do not have to be set out in lines. They are simply planted wherever there appears to be ample room for them to grow.

According to Noel,[17] the principal factor influencing the growth of the nutmeg tree is the amount of rainfall which should be well distributed and at least 80 in. per year. Optimum conditions in this respect prevail at elevations of from 600 to 800 ft., in the center of the island. The tree does not grow in the coastal plains.

Nutmeg trees bear the first fruit four years after planting, but the first commercial harvest takes place only after sixteen years. The trees continue bearing fruit for a hundred years and perhaps more.

It is estimated that there are about 10,000 acres devoted to the cultivation of nutmegs in Grenada. Large plantations comprise approximately 70 per cent of this acreage, the remaining 30 per cent being plots of from 1 to 5 acres in the hands of small farmers. Out of a population of 70,000, about 14,000 are such farmers.

Whereas in the Far East the fruits are usually picked from the tree before the husk splits, in Grenada the husk is allowed to split while the fruit is still on the tree, and the ripe fruit is collected from the ground. If the fruits are not picked up quickly, the nutmegs become waterlogged and ferment or start to grow, and weevils and worms enter the shell.

Nutmeg trees produce fruit all year round, but most heavily in August and September, and from February to April, inclusive. In June, November, and December collections are lightest. The productivity of a tree depends upon ecological (primarily soil) conditions and upon its vigor (plant selection). According to information gathered by the author during a visit to Grenada, the yield ranges from a few pounds of dried nutmegs to as many as 100 lb. per tree. Whitaker[18] reports that in Grenada the trees average

[16] *U. S. Dept. Commerce, Foreign Commerce Weekly*, Washington, D. C. 25 (November 23, 1946), 7. Cf. *Spice Mill* 71, No. 5 (1948), 51.

[17] Author's conversation with Mr. Carlyle Noel, Grenville, Grenada, and Mr. William O'Brien Donovan, St. George, Grenada.

[18] *U. S. Dept. Commerce, Foreign Commerce Weekly*, Washington, D. C. 25 (November 23, 1946), 7. Cf. *Spice Mill* 71, No. 5 (1948), 51.

about 1,000 nutmegs per year and that a tree in full bearing produces about 50 lb. of green nutmegs per year. An acre of nutmeg trees contains perhaps 90 or 100 trees. Many of these are young, not yet in full bearing or indeed not bearing at all, and some are past their prime. On a number of estates the less prolific young trees are cut out from time to time. The return per acre averages 1,500 lb. of green nutmegs a year—which, when dried and removed from the shells, yield about 720 lb. of sound nuts.

The yield of mace averages 150 lb. of green, or 30 to 40 lb. of cured, mace per acre. Ordinarily it takes about 100 lb. of green nutmegs to yield 8 lb. of fresh mace.

Total yearly production of nutmegs in Grenada averages 6,000,000 lb., that of mace 600,000 lb.

The Grenada Co-Operative Nutmeg Association advises its members never to collect or harvest the fruit prior to the natural opening of the "husk," considering it an absolutely unsound policy to "reap" fruit from the trees. Only fully ripened fruit fallen to the ground should be gathered, and this, under favorable weather conditions, within 24 hr. after their fall. Immature nutmegs result in a very low-grade spice. The work of collecting the fruit is done only once a day by women and children who go through the orchards. The gathered fruit (or the nutmegs for that matter) should never be heaped, as this may cause fermentation or sweating of the nutmegs and mold development. The soft husk is removed from the core, and the mace separated from the shell containing the nutmeg. Mace and nutmegs (the latter still within their shells) are then placed in separate baskets and brought to the "boucans" (curing houses) for drying. Here women flatten the pieces of mace and later spread them about 1 in. deep on large trays to dry in the sun for about 48 to 60 hr. When thoroughly dried, the mace—now reddish-brown and brittle—is packed away in large bins measuring about 6 ft. in each direction, where it is sealed tightly and kept from the ravages of the mace weevil by regular carbon bisulfide fumigation. A few teaspoonfuls of this chemical placed in a little saucer in the top of the bins every few days keep insects and mice away. After about five months the mace turns to a deep yellow color, about the shade of flint corn. At this stage it is ready to be prepared for export. For this purpose it is taken out of the storage bins and assorted by hand. In the cleaning process, mace is first sifted in a large mechanical oscillating sifter, then picked over by women experienced in this work. The large clear yellow pieces constitute the highest grade, or "pale whole mace." The darker colored pieces, somewhat smaller in size, are classified as "No. 1 broken grade," the small, dark-colored pieces as "No. 2 broken." Chaff and dark bits, stained from lying too long in the fields or in water, or which have some malformation, are put aside as an inferior type—"mace pickings"—

and seldom sold in the United States. After being sorted, mace is packed by hand according to grade in light plywood cases similar to tea chests, each containing 200 lb.

As regards nutmegs, they are dried (cured) while still enclosed in their shiny dark-brown shells, then removed (by cracking) from the shells, but only on orders for shipment of the spice. This helps to protect the kernels (nutmegs) against infestation by insects. As a general rule, the nuts are best cured in the air and away from sunshine, but such a procedure can be carried out only in buildings with an efficient system of aeration. The nuts are placed on shallow trays under cover, being spread no deeper than 3 in.; if spread more thickly they are liable to ferment or cure improperly. Some drying frames are 20 ft. long and 10 ft. wide; the drying sheds or "boucans" may be as large as 60 to 80 ft. long and 30 ft. wide. During the drying the nuts must be stirred two or three times a day with a long-handled hoe, to insure proper ventilation. A good product can be obtained in six weeks' time if only freshly fallen fruits are gathered within 24 hr. of their fall, and cured in the manner now usually employed, viz., aired for seven days; then exposed to early morning sunshine until about 9:30 A.M.—this for ten days; then to daily sunshine in the morning until not later than 11:30 A.M., and in the afternoon for about 1½ hr., until 5 P.M.—this for fourteen days; and finally ½ hr. of sunshine every morning—this for twelve days (with turning twice daily for each of these treatments). After about six weeks of curing, the dried nuts are shoveled into bags and stored in a clean, well-ventilated place to await shipment. In this stage the nutmeg is still enclosed in its shell, approximately a quarter of an inch longer and wider than the kernel (nutmeg) itself. Just prior to shipment, the nuts are taken out of the bags, one bag at a time, and dumped on a clean wooden floor. Women with small wooden hammers rapidly crack the shells surrounding the kernels. The nutmegs are then dumped into tanks filled with water, and slowly stirred. Those floating are considered "grinders" or "defectives," and employed for distillation purposes; nutmegs that sink to the bottom of the tank are considered "sound, unassorted" nutmegs, suitable as food. Both types are thoroughly dried in the air, carefully picked over, and finally exported from St. George, the only shipping port on the island of Grenada. Export of the spice is now a monopoly of the Grenada Co-Operative Nutmeg Association, with headquarters in St. George.

For shipment to England, Grenada nutmegs are graded in 60's, 65's, 80's, 110's and 130's—these numbers referring to the quantity of nuts per pound. When shipped to the United States they are not graded for size, but simply divided into two classes, "sound" nutmegs (used principally in food), and "defectives" (employed only for the distillation of nutmeg oil).

All nutmegs imported into the United States must meet standards set by the Pure Food and Drug Administration. The bulk of nutmeg oil produced in Europe and in the United States is derived from imported spice. However, a few years ago Grenada began local distillation of small quantities. Since nutmegs are available for the entire year, the oil is distilled at all seasons from both the shells and defective nuts. In 1946 there was only one still on the island for the distillation of nutmeg oil, but production could be largely increased by using rum stills or importing other stills. This would allow utilization of nutmeg shells, now a waste product. The bulk of nutmeg oil produced in Grenada goes to England. In 1945 about 3,100 lb. of oil were produced on the island; of this quantity 2,584 lb. went to the United Kingdom and 540 lb. to the United States. In 1946 the exports of nutmeg oil from Grenada amounted to 7,065 lb.[19]

The Fixed Oil.—Among other constituents nutmegs contain from 25 to 40 per cent of fixed oil, also known as concrete or expressed oil, or nutmeg butter (*Oleum myristicae expressum*). This is an orange-colored mass, very aromatic and of butter-like consistency at room temperature. The oil can be obtained by expressing crushed nutmegs between heated plates in the presence of steam, or by extracting with a volatile solvent.

Power and Salway[20] found that fixed oil of nutmeg contains 73 per cent of trimyristin (glyceryl myristate), 12.5 per cent of essential (volatile) oil, 3.5 per cent of fat (glyceryl oleate and linoleate), 2 per cent of resin, minute quantities of formic, acetic and cerotic acids, and 8.5 per cent of unsaponifiable residue.

The fixed oil is of no culinary interest, but may be used to a limited extent in medicinal preparations, particularly in mild stimulants for external application. According to Redgrove,[21] the fixed oil was at one time highly favored for the preparation of certain hair tonics.

It should be mentioned here that it is very difficult to remove the volatile oil from the fixed oil by distillation: the latter oil retains the volatile oil quite tenaciously through reduction of vapor pressure and vaporization rate (cf. Vol. I of the present work, p. 162).

The Volatile (Essential) Oil.—As was mentioned above, both nutmeg and mace contain a volatile oil which can be isolated by steam distillation. The yield of oil varies greatly with the geographical origin of the spice and with its quality; hence it is difficult to give average figures. Wormy nutmegs, e.g., in commercial distillation give a much better yield of volatile oil than do sound nutmegs, for the simple reason that in the former most of the fixed (fatty oil) has been devoured by the worms, while the strongly aro-

[19] *Bull. Imp. Inst.* 46 (1948), 167, 173.
[20] *J. Chem. Soc.* 93 (1908), 1653.
[21] "Spices and Condiments," London, Pitman and Sons, Ltd. (1933), 295.

matic volatile oil remains intact. Sound nutmegs, on the other hand, retain all their fixed oil, and the latter, on distillation, tends to retain the volatile oil, thus lowering its yield (see above).

In odor, flavor, physicochemical properties and chemical composition, the volatile oils of nutmeg and mace are so similar that the trade usually draws no distinction between them. Since mace is generally more expensive than nutmeg (particularly broken and wormy nutmeg), the essential oil is produced mostly from the latter, and only seldom from mace.

Distillation and Yield of Oil.—Prior to distillation, the nutmegs must be comminuted, and if *sound* nutmegs are to be used, most of the fixed oil must be removed by expression. In this latter event, however, the fixed oil will dissolve much of the volatile oil present in the nuts, and on distillation of the chopped and pressed nutmegs a low yield of volatile oil will be obtained. A more suitable, and incidentally much more economical, raw material is therefore the quality known in the trade as "broken and wormy," consisting of refuse and low-priced nutmegs, from which worms have removed much of the fixed oil.

Clevenger [22] found that shriveled East Indian nutmegs give a much larger percentage of volatile oil than do the mature sound ones. The same author also observed that the loss of volatile oil from *ground* mace or nutmegs is relatively rapid, amounting to approximately 80 per cent in two months. For this reason the material should be distilled immediately after grinding.

Gildemeister and Hoffmann [23] reported a yield of volatile oil ranging from 7 to 16 per cent for nutmegs, and from 4 to 15 per cent for mace. In the author's own experience, the yield of oil depends greatly upon the origin, condition, and age of the spice; in the case of nutmegs it varies between 6 and 16 per cent. Mace gives about 10 per cent of volatile oil.

Distillation of the comminuted material is best carried out with live steam; cohobation of the distillation waters may be necessary. With a low pressure steam, about 80 per cent of the oil distills during the first 2 hr.; the balance of the oil requires up to 10 hr. to distill over. High-pressure or superheated steam should not be employed as it carries over some of the fixed oil present in the spice.

Physicochemical Properties of Oil of Nutmeg

Oil of nutmeg is a mobile, almost colorless or pale yellow liquid, possessing an odor and flavor characteristic of the spice, especially on dilution. With the passage of time the oil takes up oxygen and partly resinifies, becoming more viscous.

[22] *J. Assocn. Official Agr. Chem.* 18 (1935), 611.
[23] "Die Ätherischen Öle," 3d Ed., Vol. II, 596.

The physicochemical properties vary within quite wide limits, depending upon the origin and quality of the spice and the method of distillation. Thus the properties of the oils derived from East Indian nutmegs differ substantially from those of the oils distilled from West Indian nutmegs. Compared with the first, the West Indian type of oil exhibits a lower specific gravity, refractive index, and evaporation residue, and a higher optical rotation. This is the result chiefly of the predominance of terpenes in the West Indian oil. For the same reason the odor and flavor of the East Indian oil are much more pronounced and more characteristic of the spice than those of the West Indian type. The United States Pharmacopoeia, Fourteenth Revision, admits both oils, but requires that the label indicate whether the myristica (nutmeg) oil is of East Indian or West Indian origin.

A. East Indian Oil.—Gildemeister and Hoffmann[24] reported these properties for nutmeg oils, apparently of East Indian origin:

Specific Gravity at 15°	0.865 to 0.925
Optical Rotation	+8° 0′ to +30° 0′
Refractive Index at 20°	1.479 to 1.488
Acid Number	Up to 3.0
Ester Number	2 to 9
Ester Number after Acetylation	25 to 31
Solubility	Soluble in 0.5 to 3 vol. of 90% alcohol
Evaporation Residue	1 to 1.5 per cent, if 5 g. of oil are slowly evaporated for 12 to 15 hr., until the weight of the evaporation residue is constant
Boiling Range	On distillation in a fractionation flask, about 60 per cent of the oil distills below 180°

Genuine East Indian nutmeg oils distilled by Fritzsche Brothers, Inc., New York, from imported nutmegs of various quality, had properties ranging within the following limits:

Specific Gravity at 25°/25°	0.880 to 0.913
Optical Rotation	+7° 53′ to +22° 10′, usually above +10°. Several lots of old nutmegs produced oils having abnormally low rotations, as low as +4° 46′
Refractive Index at 20°	1.4776 to 1.4861
Evaporation Residue	0.3 to 2.1%
Solubility at 20°	Soluble in 1 to 2.5 vol. and more of 90% alcohol

As regards the evaporation residue of the oil and method of determination, see Vol. I of the present work, pp. 259, 260.

[24] *Ibid.*

Clevenger [25] reported these properties for a number of oils distilled from Banda nutmegs (I), Padang nutmegs (II), and shriveled East Indian nutmegs (III):

	I	*II*	*III*
Yield of Oil (cc. per 100 g. of spice)	4 to 10	8 to 11.5	11.5 to 21.0
Specific Gravity at 20°/20°	0.919 to 0.956	0.878 to 0.909	0.897 to 0.916
Optical Rotation at 20°	+11° 42′ to +20° 36′	+20° 42′ to +27° 42′	+19° 18′ to +21° 48′
Refractive Index at 20°	1.483 to 1.495	1.476 to 1.481	1.479 to 1.482
Acid Number	2.5 and 8.8	1.2 and 2.4	2.46
Ester Number	13.8 and 19.7	6.0 and 11.2	12.3

Clevenger [26] arrived at the conclusion that the volatile oils obtained from ground nutmegs and mace that have been exposed in the laboratory exhibit a definite increase in specific gravity, refractive index, acid and ester numbers, and a distinct decrease in optical rotation. These observations should prove valuable in determining the conditions under which these products are to be handled.

Distilling *fresh* (undried) East Indian nutmegs, de Jong [27] obtained an oil with the following properties:

Specific Gravity at 20°	0.940
Optical Rotation at 20°	+10° 20′
Boiling Range at atm. pr.	155° to 175°—9.5% 175° to 200°—37% 200° to 250°—22.0% 250° to 285°—27.0%

An experimental distillation, on a commercial scale, of Ceylon nutmegs by Fritzsche Brothers, Inc., New York, gave an oil with the following properties:

Specific Gravity at 25°/25°	0.873
Optical Rotation	+28° 55′
Refractive Index at 20°	1.4765
Evaporation Residue	1.0%
Solubility	Soluble in 3 vol. of 90% alcohol and more

B. West Indian Oil.—Genuine West Indian nutmeg oils distilled by Fritzsche Brothers, Inc., New York, from imported nutmegs of various quality, had properties ranging within these limits:

[25] *J. Assocn. Official Agr. Chem.* **18** (1935), 614.
[26] *Ibid.*
[27] *Teysmannia* (1907), No. 8. Cf. *Ber. Schimmel & Co.*, October (1908), 91.

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umber of oils distilled from
d shriveled East Indian nut-

	II	III
	8 to 11.5	11.5 to 21.0
	0.878 to 0.909	0.897 to 0.916
	+20° 42′ to +27° 42′	+19° 18′ to +21° 48′
	1.476 to 1.481	1.479 to 1.482
	1.2 and 2.4	2.46
	6.0 and 11.2	12.3

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Soluble in 3 vol. of 90% alcohol and more

Indian nutmeg oils distilled by
m imported nutmegs of various
ese limits:

l & Co., October (1908), 91.

Specific Gravity at 25°/25°	0.859 to 0.865
Optical Rotation	+25° 45′ to +38° 32′
Refractive Index at 20°	1.4729 to 1.4746
Evaporation Residue	0.2 to 0.8%
Solubility at 20°	Soluble in 2 to 3 vol. of 90% alcohol and more

Clevenger[28] reported the following properties for a number of oils distilled from West Indian nutmegs:

Yield of Oil (cc. per 100 g. of spice)	8.5 to 10.0
Specific Gravity at 20°/20°	0.859 to 0.868
Optical Rotation at 20°	+40° 48′ to +49° 48′
Refractive Index at 20°	1.469 to 1.472
Acid Number	1.0 and 1.3
Ester Number	6.8 and 7.3

According to Clevenger,[29] West Indian nutmegs and mace yield volatile oils which may be distinguished from the corresponding East Indian oils by their low specific gravities and refractive indices, and high optical rotations.

Nutmegs imported from Grenada (B.W.I.) and distilled in the Imperial Institute, London,[30] yielded about 11 per cent of volatile oil with these properties:

	I	II
Specific Gravity at 15.5°/15.5°	0.8666	0.8682
Optical Rotation at 25°	+48° 42′	+48° 24′ (at 24°)
Refractive Index at 20°	1.4728	1.4736
Solubility at 15.5°	Soluble in 4 vol. of 90% alcohol, with slight opalescence	

These properties demonstrate that the West Indian nutmeg oils differ markedly from the East Indian oils. The odor of the former is weaker, less characteristic and spicy than that of the East Indian oils. This difference results from the fact that West Indian oils contain a larger amount of terpenes, which lower their quality.

Physicochemical Properties of Oil of Mace

Odor and flavor, as well as physicochemical properties of mace oil, closely resemble those of nutmeg oil (see above). On exposure to the air, the oil partly resinifies and takes on a turpentine-like, rather disagreeable odor.

[28] *J. Assocn. Official Agr. Chem.* 18 (1935), 613.
[29] *Ibid.*, 615.
[30] *Bull. Imp. Inst.* 35 (1937), 289.

A. East Indian Oil.—Gildemeister and Hoffmann [31] reported the following properties for mace oils, apparently of East Indian origin:

Specific Gravity at 15°	0.890 to 0.930
Optical Rotation	+10° 0′ to +22° 0′
Solubility	Clearly soluble in 2 to 3 vol. of 90% alcohol

Distilling East Indian mace from Banda (I) and from Padang (II), Clevenger [32] obtained volatile oils with these values:

	I	*II*
Yield of Oil (cc. per 100 g. of spice)	10.4 to 16.4	17.0 to 27.0
Specific Gravity at 20°/20°	0.923 to 0.947	0.917 to 0.936
Optical Rotation at 20°	+2° 42′ to +11° 48′	+7° 36′ to +11° 24′
Refractive Index at 20°	1.486 to 1.494	1.485 to 1.491
Acid Number	2.0 to 3.9	1.4 to 3.0
Ester Number	1.2 to 7.3	3.5 to 8.5

Clevenger [33] noted that volatile oils distilled from mace exhibit a lower dextrorotation than oils derived from nutmegs of corresponding geographical origin. This may be the result of the loss, in mace, of the more volatile fractions of oil, which have a high dextrorotation.

B. West Indian Oil.—Clevenger [34] also distilled a number of oils from West Indian mace and reported the following properties:

Yield of Oil (cc. per 100 g. of spice)	8.5 to 15.0
Specific Gravity at 20°/20°	0.860 to 0.892
Optical Rotation at 20°	+21° 18′ to +41° 30′
Refractive Index at 20°	1.472 to 1.479
Acid Number	1.5 to 6.2
Ester Number	2.8 to 12.8

As in the case of the nutmeg oils, the West Indian mace oils exhibited lower specific gravities and refractive indices and higher optical rotations than the East Indian mace oils. Odor and flavor of the former type of oil are inferior to those of the East Indian oils.

Chemical Composition of Nutmeg and Mace Oil

Oils of nutmeg and mace are so similar that their chemical composition can be discussed in one section. In fact, a number of researchers in the past did not clearly define the origin of the oil which they examined.

The earliest investigations of nutmeg (or mace) oil date back to the first

[31] "Die Ätherischen Öle," 3d Ed., Vol. II, 597.
[32] *J. Assocn. Official Agr. Chem.* 18 (1935), 614.
[33] *Ibid.*
[34] *Ibid.*

decades of the past century, but were so inconclusive that they require no discussion.[35] We owe our present knowledge of the chemical composition of this oil chiefly to the work of Wallach,[36] Semmler,[37] Thoms,[38] Power and Salway,[39] and Schimmel & Co.[40] These investigators have reported the presence of the following compounds (listed approximately according to their boiling points):

d- and *l*-α-Pinene. As far back as 1862 Schacht [41] observed in oil of mace a hydrocarbon which gave a solid hydrochloride; he named this hydrocarbon "Macene." Years later, Wallach identified "Macene" as α-pinene (nitrolbenzylamine m. 123°). It occurs in the lowest boiling fraction of the oil as an optically almost inactive mixture of *d*- and *l*-α-pinene.

Camphene. Identified by Power and Salway, who hydrated the terpene to isoborneol m. 207°–212° (phenylurethane m. 138°).

β-Pinene. Present only in small quantities. Characterized by oxidation to nopinic acid m. 126°–128° (Schimmel & Co.).

Dipentene. Identified by means of its tetrabromide m. 124°–125° (Wallach; Power and Salway; and Schimmel & Co.).

p-Cymene. Characterized by oxidation to *p*-hydroxyisopropylbenzoic acid m. 155°–156° (Schimmel & Co.).

d-Linaloöl. Oxidation to citral, the latter identified by preparation of the α-citryl-β-naphthocinchoninic acid m. 200° (Power and Salway).

l-Terpinen-4-ol. Identified in the fraction b. 205°–215° (Schimmel & Co.).

Borneol. Oxidizing the fraction b. 205°–215°, Power and Salway, among other products, obtained camphor (semicarbazone m. 238°); it was probably formed by oxidation of borneol originally present in the oil.

dl-α-Terpineol. The same authors also noted that the oil contains *dl*-α-terpineol, which they characterized by preparation of dipentene dihydroiodide m. 80°, and by oxidation to the ketolactone $C_{10}H_{16}O_3$, m. 62°–63°.

About eighty years ago Wright [42] expressed the opinion that the oil contains an alcohol b. 212°–218°, to which he referred as "Myristicol." In reality this alcohol is a mixture of l-terpinen-4-ol, borneol, and α-terpineol.

Geraniol. Identified by means of its diphenylurethane m. 81°-82° (Power and Salway.)

Safrole. Characterized by oxidation to piperonal m. 31°–35° (Power and Salway).

[35] For a listing of these publications, see Gildemeister and Hoffmann, "Die Ätherischen Öle," 3d Ed., Vol. II, 598, footnote 1.
[36] *Liebigs Ann.* 227 (1885), 288; 252 (1889), 105.
[37] *Ber.* 23 (1890), 1803; 24 (1891), 3818.
[38] *Ber.* 36 (1903), 3116.
[39] *J. Chem. Soc.* 91 (1907), 2037. (These two authors used a "normal" and a "heavy" [i.e., rectified] oil in their investigations.)
[40] *Ber. Schimmel & Co.*, April (1910), 75.
[41] *Arch. Pharm.* 162 (1862), 106.
[42] *J. Chem. Soc.* 26 (1873), 519.

An Aldehyde(?). The substance in question had an odor reminiscent of citral and yielded a β-naphthocinchoninic acid compound m. 248°. Its identity, however, was not established (Power and Salway).

Myristicin. This phenolic ether $C_{11}H_{12}O_3$ occurs in the highest boiling fractions of nutmeg and mace oils. It is one of the most important constituents of the oils. The chemical constitution of myristicin was elucidated by Thoms.[43] (For details, see Vol. II of the present work, p. 531.) Myristicin is toxic and acts as a narcotic. When taken in sufficient quantities, it is liable to cause fatty degeneration of the liver.

The oil also contains several phenols, of which Power and Salway identified:

Eugenol. Benzoate m. 69°, diphenylurethane m. 107°–108°.

Isoeugenol. Benzoate m. 105°.

In the saponification lyes of the oil Power and Salway noted the presence of these acids:

Formic Acid. Identified as barium salt.

Acetic Acid. Identified as barium salt.

Butyric Acid. Identified as barium salt.

***n*-Caprylic Acid.** Identified as silver salt.

A Monocarboxylic Acid $C_{12}H_{17}OCOOH$. Nonvolatile, insoluble in water; m. 84°–85°.

Myristic Acid. M. 54°; present in the oil free and esterified. Depending upon the length of distillation and the steam pressure applied, smaller or larger amounts of this acid and its esters occur in the oil. On evaporation of the oil, the acid remains in the residue. If large quantities are present, the acid may separate from the oil in crystalline form. In the early literature this crystalline deposit was called "Myristicin." It must not be confused with true myristicin, i.e., the phenolic ether $C_{11}H_{12}O_3$ described above.

As a result of their work, Power and Salway[44] reported the following quantitative composition for the nutmeg oil which they investigated:

d-Pinene, *d*-Camphene	About 80 per cent
Dipentene	About 8 per cent
d-Linaloöl, *d*-Borneol, *dl*-Terpineol, Geraniol	About 6 per cent
1-Terpinen-4-ol[45]	Small quantities
An Aldehyde with citral odor	Traces
Safrole	About 0.6 per cent

[43] *Ber.* 36 (1903), 3446.
[44] *J. Chem. Soc.* 91 (1907), 2037.
[45] This compound identified by Schimmel & Co. (see above) appears to be identical with the alcohol found by Power and Salway, which, on oxidation, yielded a diketone $C_8H_{14}O_2$, dioxime m. 140°.

Myristicin	About 4 per cent
Eugenol, Isoeugenol	About 0.2 per cent
Myristic Acid, free	About 0.3 per cent
Myristic Esters	Small quantities
Formic Esters, Acetic Esters, Butyric Esters, *n*-Caprylic Esters, Esters of Monocarboxylic Acid $C_{13}H_{18}O_3$	Small quantities

Power and Salway emphasized that these proportions are not absolute; in fact, they vary greatly with the quality and origin of the spice from which an oil is derived. The oil investigated by Power and Salway (d_{15} 0.869, α_D +38° 4′) was distilled from Ceylon nutmegs. Its relatively low specific gravity and elevated optical rotation permit the conclusion that the oil was particularly rich in terpenes. In other nutmeg oils the content of oxygenated compounds is probably much higher than in the oil examined by Power and Salway.

Use of Nutmeg and Mace Oils

Oil of nutmeg and the almost identical oil of mace are used widely for the flavoring of numerous food products, particularly baked goods, cakes, cookies, custards, puddings, pickles, etc. The oils find application also in table sauces, tomato catsup, and all kinds of savory preparations and dishes. If well blended, they lend a pleasant smoothness to flavor combinations.

As Power and Salway[46] found, oils of nutmeg and mace are somewhat poisonous, the toxicity being caused by the presence of myristicin (see above). In pharmaceutical preparations—the oil has been recommended for treatment of inflammations of the bladder and urinary tract[47]—large doses must be avoided.

Oil of nutmeg is used also in certain types of perfumes, and for the flavoring of dentifrices.

Oil of *Myristica Fragrans* Houtt., from the Leaves

Meyer[48] steam-distilled dried leaves of the true nutmeg tree *Myristica fragrans* Houtt., and obtained 1.56 per cent of a colorless volatile oil with these properties:

[46] *Am. J. Pharm.* 80 (1908), 563.
[47] Führer, *Med. Welt* 30 (1910), 779. *Merck's Jahresber.* 55 (1913), 157.
[48] *Ing. Nederland-Indië* 8 (1911), No. 1, VII, 7. *Chem. Abstracts* 35 (1911), 4549.

effects were varied but marked, that they must voluntarily affirm their wish to participate by raising their hands and that should they experience any difficulty they must say so at once.

All groups were then told that the substance/drug had a characteristic odour which had been concealed by mixing it with ordinary spices. Members of HSN and LSN groups then consumed about 6g ground nutmeg mixed with a liberal quantity of diluted anchovy essence, whilst the placebo groups took a similar volume of gravy browning in anchovy essence. A number of hard letter series problems[3] were then displayed and the subjects were required to solve them, setting down their answers and the time taken to solve the problem, and any change in their experience which occurred. After 45 min at these tasks the subjects were issued with a sheet which asked them to underline one of a series of five statements describing the problems, ranging from "very difficult indeed" to "very easy". The next section of the sheet contained eight groups of statements each covering a range of subjective changes in the following categories:

(i) extreme arousal to drowsiness (9 statements)
(ii) unusual excitement and elation to marked depression (9 statements)
(iii) indigestion to near vomiting (6 statements)
(iv) striking increase in visual clarity and improvement in colours to dullness of colours and blurring of vision (9 statements)
(v) seeming quickness and sureness of movement to clumsiness and impairment (7 statements)
(vi) stiffness or twinges of discomfort to stabbing pains (6 statements)
(vii) thinking with unusual facility to marked interference of thought (7 statements)
(viii) depersonalisation experiences (3 statements).

The final section asked the subjects to write down any comments they wished to make.

A few days later the details of the experiment were given to the subjects after enquiries had been made of them as to their expectations, beliefs and attitudes at the time of the experiment.

RESULTS

Hypothesis (i)

All estimates of problem difficulty used one of 3 statements ("quite hard", "not too bad", "fairly simple"). Contrasting combined drug with combined placebo conditions (21 subjects in each condition), χ^2 attains a value of 7·43 which is not significant. Drug subjects do not see problems as being easier; null hypothesis supported.

Hypothesis (ii)

The mean times taken for correct solutions were:

Drug groups, 39·0 sec Placebo groups, 37·2 sec.

The mean scores of number correct out of twenty were:

Drug groups, 14·0 Placebo groups, 13·2.

The drug had no effect on either accuracy or speed of problem solving; null hypothesis confirmed.

55a

Oil of Monarda. Oil of horsemint. Volatile oil from *Monarda punctata* L., *Labiatae*. *Constit.* About 60% thymol; considerable cymene, some *d*-limonene, carvacrol, linalool. Yellowish-red to brownish liq; mint odor; thyme-like taste. d_{15}^{15} 0.930–0.940. Slightly dextrorotatory. Sol

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Merck Index 8th Ed. 1968

ild marjoram. Volatile oil from
ulgare L., *Labiatae*. *Constit.*

0.870–0.910. Rotation about
ater; very sol in alcohol. *Keep*
d from light.
alled "Oil of Origanum" is oil

. Volatile oil from *Origanum*
. Carvacrol, cymene terpenes.
dark brown to grayish-black
4–0.98. Optically inactive or

oil from parsley seeds *Petro-*
atticum Hoffm., *Carum petro-*
belliferae. *Constit.* Chiefly

iscid liquid. d_{15}^{15} 1.040–1.100.
0-mm tube. n_D^{20} 1.510–1.519.
. . . . . sol in water; sol in 8 vols 80% alcohol; sol in ether.

. . . . . About
. . . . . terpineol, limonene and *d*-pinene

Slightly yellow liq; aromatic odor; pungent, refreshing, peppermint-like taste. d_{15}^{15} 0.908–0.932. Inactive or slightly dextro- or levorotatory. Insoluble in water or glycerol; sol in alcohol, benzene, ether.

MED USE: Has been used as vermifuge, expectorant.

Oil of Nutmeg, Expressed. Nutmeg butter; oil of mace. Oil expressed from nutmeg (*Myristica fragrans* Houtt., *Myristicaceae*). *Constit.* Chiefly trimyristin; some volatile oil.

Orange-red to reddish-brown, soft solid; odor and taste of nutmeg. d 0.990–0.995. mp 45–51°. Sapon no. 172–179. Iodine no. 40–52. Acid no. 17–23. Partly sol in cold alcohol, almost completely in hot alcohol; freely sol in chloroform, ether.

MED USE: Formerly as rubefacient. *Human Toxicity: See* Oil of Nutmeg, Volatile.

Oil of Nutmeg, Volatile. Oil of myristica. Steam-distilled oil from dried kernels of ripe seeds of nutmeg (*Myristica fragrans* Houtt., *Myristicaceae*). *Constit.* 60–80% *d*-Camphene, about 8% *d*-pinene; dipentene, *d*-borneol, *l*-terpineol, about 6% geraniol, safrol, about 4% myristicin.

Colorless or pale yellow liq; odor and taste of nutmeg. d_{25}^{25} 0.859–0.924. Rotation +10° to +30° in 100-mm tube. n_D^{20} 1.4740–1.4880. Insoluble in water; sol in 1 vol alcohol, in 3 vols 90% alcohol. *Keep well closed, cool, and protected from light.*

USE: As a flavor.

MED USE: Carminative. *Human Toxicity:* Ingestion of large quantities produces narcosis, delirium, death.

Oil of Orange. Oil sweet orange. Volatile oil expressed from fresh peel of ripe fruit of the orange (*Citrus aurantium* var *sinensis* L., *Rutaceae*). *Constit.* About 90% *d*-limonene; citral, decyl aldehyde, methyl anthranilate, linalool, terpineol.

Yellow to deep orange liq; characteristic orange taste and odor. d_{25}^{25} 0.842–0.846. Rotation +94° to +99° in 100-mm tube at 25°. n_D^{20} 1.4723–1.4737. Slightly sol in water; sol in 2 vols 90% alcohol 1 vol glacial acetic acid; miscible with abs alcohol, carbon disulfide. *Keep well closed, cool, and protected from light.*

USE: Chiefly as flavor and perfumic.

MED USE: Formerly as expectorant.

Oil of Orange Flowers. Oil of neroli. Volatile oil distilled from fresh orange flowers. *Constit.* Limonene, *l*-linalool, geraniol, 7–15% linalyl acetate; some methyl anthranilate, nerol and neroli camphor.

Yellowish, fluorescent liq; very intense and pleasant odor; becomes brown on exposure to light. d_{25}^{25} 0.86–0.88. Rotation +1° 30′ to +9° 8′ in a 100-mm tube at 25°. n_D^{20} 1.475. Slightly sol in water; sol in 1.5–2 vols 80% alcohol with fine violet fluorescence. *Keep well closed, cool, and protected from light.*

USE: As perfume and flavor.

Oil of Patchouly. Patchouli oil. Essential oil from leaves of the cultivated *Pogostemon cablin* (Blanco) Benth. (*P. patchouly* Pellet. var *suavis* Hook. f.), *Labiatae*, sometimes mixed with oil from the wild growing *Pogostemon heyneanus* Benth., *Labiatae*. *Review:* E. Guenther, *The Essential Oils* vol. III, 552–575 (Van Nostrand, New York, 1949). *Constit.* Patchouly alc, patchoulene, azulene, cadinene(?), eugenol, benzaldehyde, cinnamic aldehyde, several unidentified ketones, sesquiterpenes, and sesquiterpene ales: Pfau, Plattner, *Helv. Chim. Acta* 19, 874 (1936), *see also* Patchouly Alcohol.

Yellowish or greenish to dark brown oil, intense and persistent fragrant odor. Can be stored indefinitely. Odor seems to improve with age. d_{15}^{15} 0.975–0.987. $[\alpha]_D^{20}$ −54° to −65.3°. n_D^{20} 1.5099 to 1.5111. Saponification number 3.3 to 9.3. Ester number after acetylation: 17.7 to 22.4. Practically insol in water. Soluble in 0.5 vol of 90% alcohol. Soluble in ether.

USE: In perfume formulations to impart a lasting oriental fragrance, in incense, soaps, cosmetics. To scent fine Indian fabrics and shawls.

Oil of Pennyroyal—American. Oil of hedeoma. Volatile oil from leaves and flowering tops of *Hedeoma pulegioides* (L.) Pers., *Labiatae*. *Constit.* Chiefly pulegone; 2 ketones; acetic, formic and isoheptoic acids.

Pale yellow liq; aromatic odor. d_{25}^{25} 0.920–0.935. Rotation +18° to +22° in a 100-mm tube at 20°. n_D^{20} 1.482. Slightly sol in water; sol in 3 vols 70% alcohol; very sol in chloroform, ether. *Keep well closed, cool, and protected from light.*

MED USE: Formerly as aromatic carminative.

Oil of Pennyroyal—European. Oil of pulegium. Volatile oil from *Mentha pulegium* L., *Labiatae*. *Constit.* About 85% pulegone.

Yellow or greenish-yellow; aromatic mint-like odor; aromatic taste. d_{15}^{15} 0.960. Rotation +14° to +28° in a 100-mm tube at 20°. n_D^{20} 1.475–1.496.

Human Toxicity: May cause abortion.

Oil of Pepper. Volatile oil from unripe fruit of the black pepper. *Constit.* Chiefly *l*-phellandrene, sesquiterpenes (caryophyllene).

Colorless or yellowish liquid. d_{15}^{15} 0.890–0.900. n_D^{20} 1.4935–1.4977. Rotation about −3° to −5°. Insoluble in water; sol in about 15 vols 90% alcohol.

USE: As condiment.

Oil of Peppermint. Steam-distilled, volatile oil from fresh flowering plant *Mentha piperita* L., *Labiatae*. The Japanese oil, also known as oil of Poho, is the liq portion remaining after the separation of menthol from the oil of *Mentha arvensis* L., *Labiatae*. *Constit.* Not less than 50%

(76)

Kryptoäscin A ist also ein Substanzgemisch von mindestens sieben Komponenten, das als wesentliche Bestandteile (40%) Äscin und Äscinmethylester enthält. Die Umwandlung von Kryptoäscin A im Kryptoäscin B ist nur als ein Reinigungsprozeß aufzufassen. Wir danken der Fa. A. Klinge und Co., München, für die Überlassung von Kryptoäscin A und B.

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RUDOLF TSCHESCHE und UDO AXEN

Eingegangen am 14. Februar 1964

[1]) XIV. Mitteilung: TSCHESCHE, R., E. HENCKEL u. G. SNATZKE: Liebigs Ann. Chem. (im Druck). — [2]) WAGNER, J., u. J. BOSSE: Hoppe-Seyler's Z. physiol. Chem. 322, 254 (1960). — [3]) KUHN, R., u. I. LÖW: a) Liebigs Ann. Chem. 669, 183 (1963); b) Tetrahydron Letters 15, 891 (1964). — [4]) Herrn Prof. KUHN danken wir sehr für die Überlassung von Vergleichssubstanzen und für die freundliche Mitteilung noch unveröffentlichter Ergebnisse. — [5]) TSCHESCHE, R., U. AXEN u. G. SNATZKE: Liebigs Ann. Chem. 669, 171 (1963).

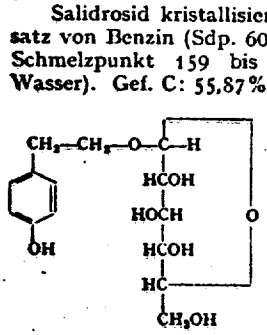
Anmerkung bei der Korrektur (8. 5. 64): Das von R. KUHN u. I. LÖW[3a,b]) aus Äscin isolierte Protoäscigenin und Äscinidin wurde auch von uns aus Äscin (Fa. Madaus) erhalten. Aus den Ergebnissen der Veröffentlichung von R. KUHN und I. LÖW[3a]) und einer Privatmitteilung von R. KUHN[4]) muß geschlossen werden, daß die Zuckerverknüpfung und die Anordnung der Fettsäuren im Äscin möglicherweise anders sind, als von U. AXEN in seiner Dissertation vorgeschlagen wurde, so daß der Strukturvorschlag für Äscin[5]) korrekturbedürftig erscheint.

Zur Konstitution des Salidrosids, eines Phenolglykosids aus Salix triandra L.

Aus der Rinde der Mandelweide (Salix triandra L.) gelang 1926 BRIDEL und BÉGUIN[1]) die Isolierung eines neuen, nicht kristallisierenden Glykosids (Salidrosid), das bei der fermentativen Spaltung mit Emulsin neben Glucose ein öliges, rosenartig riechendes Aglykon lieferte, das aus Äther/Petroläther in weniger aromatisch reichenden Blättchen kristallisierte. Die Autoren nahmen an, daß es sich dabei um ein Polymerisationsprodukt des öligen Aglykons handelt. Auch RABATÉ[2]), der das Glykosid später noch in Salix arbuscula L. und Salix glauca L. nachwies, konnte es nicht zur Kristallisation bringen und auch das Aglykon (Salidrosol), dessen Schmelzpunkt mit 92°C bestimmt wurde, nicht identifizieren.

Die Isolierung des Salidrosids aus der Rinde von Salix triandra L. gelang uns nach Abtrennung des Gesamtglykosidkomplexes [Polyamidchromatographie, kontinuierliche Extraktion mit Essigsäureäthylester[3c])] durch anschließende Chromatographie an einer Cellulosesäule (Schleicher & Schüll Nr. 123) mit dem Verteilungsmittel n-Butanol/Xylol/Wasser 2:8:8.

Salidrosid kristallisiert aus Essigsäureäthylester nach Zusatz von Benzin (Sdp. 60 bis 70°C) in kleinen Blättchen vom Schmelzpunkt 159 bis 160°C. $[\alpha]_D^{20} = -32{,}1°$ ($c = 1{,}26$; Wasser). Gef. C: 55,87%, H: 6,72%. Das Glykosid zeigt auf



Papyrogrammen mit dem Verteilungsmittel n-Butanol/Xylol/Essigsäure/Wasser (6:4:2:8) den RF-Wert 0,25 (Schleicher & Schüll 2043 b mgl, aufsteigend). Beim Besprühen mit Millons Reagenz reagiert es bereits bei Zimmertemperatur unter intensiver Rotfärbung (Substitution des Aglykons in 4-Stellung, freie phenolische Hydroxylgruppe). Auch diazotiertes Sulfanilamid gibt sofort Rotfärbung. Das Glykosid wird, wie schon von BRIDEL und BÉGUIN beobachtet, von Emulsin rasch gespalten, wobei ein an Rosen erinnernder Geruch auftritt. Als Spaltprodukt der fermentativen Hydrolyse konnte neben Glucose als Aglykon und Träger des aromatischen Geruchs 4-Hydroxyphenyläthanol (Tyrosol, Schmp. 93°C) nachgewiesen werden. Die Identifizierung des Aglykons erfolgte durch Bestimmung des Mischschmelzpunktes und durch Cochromatographie mit authentischem Material*) (Verteilungsmittel n-Butanol/Xylol/Essigsäure/Wasser 2:8:2:8). Auch die IR-Spektren von Aglykon und der Vergleichssubstanz zeigten weitgehende Übereinstimmung.

Aufgrund unserer Untersuchungsergebnisse schreiben wir dem Salidrosid ($C_{14}H_{20}O_7$, Mol.-Gew. 300,3) die Konstitution eines 2-(4-Hydroxyphenyl-)äthanol-1-β-D-glucopyranosids zu.

Wie das ebenfalls in Salix triandra L. vorkommende Triandrin[3a]) und das vor kurzem von uns aus Salix viminalis L. isolierte Vimalin[3b]) gehört auch Salidrosid zu einer Gruppe von Phenolglykosiden, die den Zucker nicht über die phenolische Hydroxylgruppe, sondern über die primäre alkoholische Hydroxylgruppe des Aglykons gebunden enthalten.

Das mit Essigsäureanhydrid-Pyridin dargestellte Pentaacetylderivat konnte nicht kristallin erhalten werden.

Nach den Beobachtungen von BRIDEL und BÉGUIN[1]) ist der Salidrosidgehalt von Salix triandra L. abhängig vom Geschlecht der Pflanzen; die Rinden männlicher Exemplare sollen glykosidreicher sein. Wir können diese Angaben bestätigen, allerdings nur in bezug auf das Vorkommen des Salidrosids. Das ebenfalls in Salix triandra L. vorkommende Triandrin ist demgegenüber in den Rinden weiblicher Pflanzen in größerer Menge enthalten. In den Mitte Dezember geernteten Rinden konnten wir (bez. auf wasserfreie Droge) bei männlichen Pflanzen 0,31% Triandrin und 0,95% Salidrosid, bei weiblichen Pflanzen 0,83% Triandrin und 0,51% Salidrosid nachweisen. Der Gehalt der Rinden an Salicin lag unter 0,01%.

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*) Herrn Dr. M. STOLL, Genf, danken wir für die Überlassung einer Vergleichsprobe.

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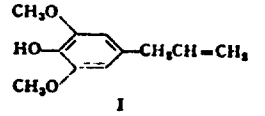
Isolation of Methoxyeugenol and *trans*-Isoelemicin from Oil of Nutmeg

Nutmeg, the seed of the tree *Myristica fragrans*, has long been known as an intoxicating substance. Attempts to assign its psychotropic effects to the myristicin content have been unsuccessful. Studies have shown this aromatic component to be inadequate in reproducing the toxic syndrome of the natural mixture[1]). The first thorough analysis of the volatile oils in nutmeg, that of POWER and SALWAY[2]), still stands as the primary reference for the identity of the many components. Recently the techniques of gas liquid chromatography have been employed in the analysis of the terpene fraction[3]) and have established the presence of elemicin[4]).

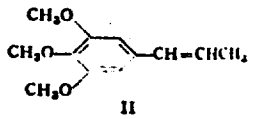
By means of fractional distillation *in vacuo*, approximately ten pounds of Oil of Nutmeg (G. Lueders and Co., U.S.P.W.I.) was separated into three fractions. Fraction A represents the combination of several distillation cuts up to 114° at 2 mm/Hg and consisted primarily of terpenes; Fraction B, b. p. 114—119° at 2 mm/Hg, was the myristicin fraction and consisted predominantly of myristicin and elemicin; Fraction C was the heavy oil obtained from the distillation residue after the removal of myristic acid by extraction with ammonium hydroxide.

Initial analysis of the latter two fractions was conducted with a G.L.C. column employing polyethylene glycol 20 M as a liquid substrate on acid-washed chromasorb W, which achieved a complete separation of elemicin and myristicin. The quantities of these components, as determined by planimetry of the recorded G.L.C. chromatograms, are listed in Table 1. In fraction B, a small following peak was observed and readily identified as isoeugenol. Fraction C revealed, in addition to these components, two slower moving peaks of a size sufficient to warrent isolation and identification.

The first of these possessed two methoxyl groups and an allyl chain (by N.M.R. analysis) as well as an exchangeable proton. The infrared spectrum was identical to that of 2,6-dimethoxy-4-allyl phenol (methoxyeugenol) (I) obtained by the Claisen rearrangement of the allyl ether of 2,6-dimethoxy phenol[5]).



I



II

This structural assignment was further confirmed by the undepressed melting point (73—74°) of the mixture of benzoates prepared separately from a synthetic sample [73.5—74°, literature value 76—77°[6])] and from the isolate from fraction C (73—74°). The infrared spectrum of the second unknown compound was identical to that obtained from the

a melting point (85.5—86.5°) undepressed (86—87°) by admixture with an authentic sample [86.5—87°, literature value 89—90°[7])].

A specific search was made for the corresponding isomerization product of myristicin, *trans*-isomyristicin, as well as for yet more highly methoxylated analogs such as are found in Oil of Parsley. G.L.C. columns were selected (silicone SE-30, silicone SF-96, and ethylene glycol succinate) which allowed each of the substances tested (*trans*-isomyristicin, 2,3,4,5-tetramethoxy allylbenzene, and apiole) to emerge at times different from the identified components of fraction C. The absence of these peaks in fraction C established the maximum concentration of these substances in Oil of Nutmeg (if present at all) as 0.005, 0.001 and 0.001%, respectively. Three trace components (representing 0.04% of the total oil) are recorded in the Table. They appear to be carbonyl-containing materials, and their structures were not determined.

Table. *Components of Oil of Nutmeg, in order of emergence from polyethylene glycol 20 M*

Component	Fraction (gms.) A	B	C	% in total orig. Oil of Nutmeg
before elemicin . . .	4055.2	5.3	1.9	90.83%
elemicin	2.5	52.4	36.9	2.05%
myristicin	26.7	195.1	16.6	5.33%
isoeugenol	2.2	6.2	0.3	0.19%
trans-isoelemicin . .	0	0	3.8	0.08%
methoxyeugenol . . .	0	0	11.0	0.25%
unidentified (after elimicin) . .	0	0	1.6	0.04%
myristic acid			55.0	1.23%

trans-isoelemicin has been previously observed in plant extracts, both in *Cymbopogon georingii* HONDA[8]) and in *Backhousia myrtifolia*[9]). Its presence in nutmeg cannot be an artifact due to accidental isomerization, for isomyristicin, which should be similarly generated from the more plentiful myristicin, is absent. Methoxyeugenol, on the other hand, has never before been observed in any natural extract. Its structural relationship to eugenol is identical to that of elemicin to methyleugenol, as well as that of myristicin to safrole, thus suggesting that its origin in nutmeg may be ascribed to existing biogenetic pathways.

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Eingegangen am 21. Februar 1964

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Über die Wirkstoffe der diaphoretischen Drogen des DAB 6

Außer den bisher bekannten Inhaltsstoffen aus den Gruppen der Hydroxyzimtsäurederivate und Flavonolfarbstoffe der Holunderblüten (Flores Sambuci DAB 6, Sambucus nigra L.) Rutin[1]), Isoquercitrin[2]), Chlorogensäure und Kaffeesäure[3]) wurden weitere Verbindungen nachgewiesen, die einer entsprechenden parallelen Reihe zugeordnet werden können. Mittels chromatographischer Vortrennung an Cellulosesäulen und weiterer aufsteigender papierchromatographischer Auftrennung, entwickelt mit Essigsäure-Wasser-Gemischen 6:4 v,v und 15:85 v,v, sowie Methanol-Wasser 1:1 v,v und Partridge-Gemisch wurden p-Cumarsäure und Astragalin (Kämpferol-3-glukosid) sowie in geringer Menge auch freies Kämpferol neben freiem Quercetin nachgewiesen. Außerdem wurde noch ein weiterer Fleck beobachtet, der jedoch aus Materialmangel bisher nicht eindeutig bestimmt werden konnte, der aber mehreren Anzeichen nach auf das Vorhandensein von Nicotiflorin hinweist.

In den offizinellen Lindenblüten von Tilia platyphyllos Scop. wurden Chlorogensäure, Kaffeesäure und p-Cumarsäure in entsprechender Weise nachgewiesen. Gegenüber den Ermittlungen von HÖRHAMMER, STICH und WAGNER[4]), die eine Reihe von Flavonolfarbstoffen aus der nicht offizinellen Tilia argentea Desf. isolierten und auch auf die offizinellen Lindenblüten übertrugen, ergaben sich geringfügige Unterschiede, die aber auf intraspezifische Differenzierungen zurückzuführen sein dürften. In den hier untersuchten Drogen gelang es nur, Glykoside des Quercetins und Kämpferols aufzufinden; die Glykoside A1 und A2 waren nicht nachweisbar.

Mit Hilfe des Keeler-Polygraphen wurde nachgewiesen, daß die Flavonolglykoside für die schweißtreibende Wirkung der untersuchten Heilpflanzen verantwortlich zu machen sind. Vermutlich wird deren Wirkung durch die Hydroxyzimtsäuren noch gesteigert. Ausführliche Angaben zu diesen Untersuchungen werden in Kürze mitgeteilt werden.

2 Hamburg-Rissen, Wedeler Landstr. 71

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Wirkung von Dinitrophenol, Azid und Anaerobiose auf die Zinkaufnahme durch Algen

Die Aufnahme von Kalium durch Pflanzenzellen, die auf aktivem Transport beruht, wird durch Anaerobiose weitgehend unterdrückt[1]), [2]). Ebenso wirken Atmungsgifte[2—4]), Offenbar genügt Adenosintriphosphat (ATP) aus der Photophosphorylierung oder aus etwaigen anaeroben Prozessen[5]), [6]) nicht als Quelle freier Energie für den aktiven Transport.

Es ist bekannt, daß nicht nur Kalium, sondern auch viele Schwermetalle durch Pflanzenzellen stark angereichert werden. Jedoch haben wir nun jedenfalls in bezug auf die Aufnahme von Zink durch *Chlorella vulgaris* festgestellt, daß der Mechanismus sich von dem der Aufnahme von Kalium grundlegend unterscheidet. Die Aufnahme von Zink wird nämlich durch die Atmungsgifte Dinitrophenol (DNP) oder Azid sowie auch durch Anaerobiose nicht beeinflußt.

Suspensionen von 310 mg *Chlorella* (Frischgewicht) in 10 ml m/10 Natriumazetat-Puffer-Lösung (pH 6,0) wurden bei Zimmertemperatur 15 Std in diffusem Licht geschüttelt. Die Lösung war in einer Reihe in bezug auf Zinkchlorid 10^{-5} molar, in einer anderen Reihe 10^{-3} molar. Das Zink in jedem Röhrchen war mit etwa 2,1 Mikrocurie Zink-65 (Halbwertszeit 245 Tage) markiert. Zu

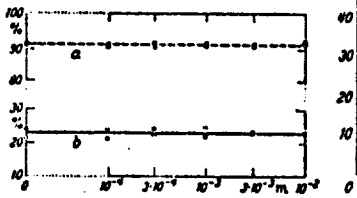

Fig. 1

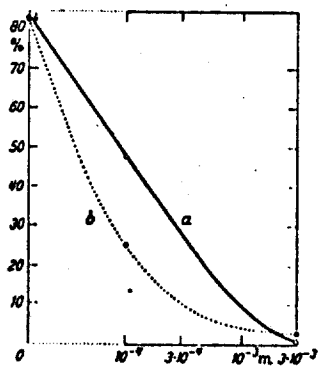

Fig. 2

Fig. 1. Abhängigkeit der Aufnahme von Radiozink durch *Chlorella* (Ordinate) von der Azid- bzw. Dinitrophenolkonzentration (Abszisse). *a* [Zn] = 10^{-5} molar; *b* [Zn] = 10^{-3} molar. ∘ Na-Azid, • Dinitrophenol

Fig. 2. Abhängigkeit der Aufnahme von Radiokalium durch *Chlorella* (Ordinate) von der Azid- bzw. Dinitrophenolkonzentration (Abszisse). *a* Na-Azid; *b* Dinitrophenol

Versuchsende wurden die Algen niedertourig abzentrifugiert, und 5 ml des Überstandes wurden mit dem Flüssigkeitszählrohr gemessen. Fig. 1 zeigt die Ergebnisse in Abhängigkeit von den Konzentrationen des DNP oder NaN_3.

In schroffem Gegensatz dazu wurde in analogen Versuchen mit Kalium-42 (Halbwertszeit 12,5 Std) starke Hemmung durch die Gifte erzielt. Die Kaliumlösung war $1{,}7 \cdot 10^{-4}$ molar, die Aktivität pro Röhrchen betrug zu Versuchsbeginn etwa 0,3 Mikrocurie, und die Versuchsdauer war 24 Std. Die

(60)

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THE COMPONENT GLYCERIDES OF NUTMEG BUTTER
(Myristica fragrans)

By S. P. PATHAK and V. N. OJHA

The component glycerides of the neutral fat extracted from nutmeg seeds (Indian name, 'Jaiphal') were studied by segregation of the fat into three fractions by crystallization from acetone and ether at 10° and 25° respectively, followed by determinations of the component acids present in each of the three fractions.

The component acids of the whole fat are dodecanoic (0·4%), tetradecanoic (71·8%), hexadecanoic (14·3%), octadecanoic (1·2%), tetradecenoic (0·8%), hexadecenoic (4·8%), octadecenoic (5·2%), and octadecadienoic (1·5%). The component glycerides are: (1) fully saturated 71·3%, (2) mono-unsaturated-disaturated 20·5% and (3) di-unsaturated-monosaturated 8·2%.

Experimental

The Jaiphal seeds were crushed and exhaustively extracted with hot acetone, which was removed by distillation. The extracted fat was shaken with light petroleum (b.p. 40-60°) to remove foreign and resinous matter, and a light-coloured fat was finally obtained amounting to 43% on weight of seeds. The fat was neutralized by washing the ethereal solution with dilute aqueous alkali.

The neutral fat (188·0 g.), having I val. 20·3 (Hanus) and acid value 0·3, was crystallized from acetone (10 ml. per g.) at 10° when 143·8 g. of glycerides (I val. 6·2) were deposited. The glycerides remaining in solution were recovered and designated as C fraction. The 143·8 g. of glycerides (I val. 6·2) were then crystallized from ether (10 ml. per g.) at 25° when 117·5 g. of glycerides (I val. 0·7) were deposited and was named fraction A; the glycerides remaining in solution were called fraction B.

The glyceride fractions A, B and C were hydrolysed and their respective mixed fatty acids recovered after removing the unsaponifiable matter with ether in the usual manner. The mixed fatty acids from fractions B and C were subjected to the lead-salt–ethanol separation method whereby fractions BA, BB, CA and CB were obtained, the results of which are recorded in Table I.

Table I

Crystallization of Jaiphal (Myristica fragrans) *glycerides*

Glyceride fractions from 188·0 g. of fat from acetone and ether (10 ml. per g. of fat)

Fraction	Description	Wt., g.	I value
A	Insoluble in ether at 25° and in acetone at 10°	117·5	0·7
B	Soluble in ether at 25°, insoluble in acetone at 10°	31·3	25·5
C	Soluble in acetone at 10°	39·2	73·6

Note: Fraction C (39·2 g.) glyceride contains 13·6 g. of unsaponifiable matter

Crystallization of fatty acids from glyceride fractions B and C by lead salt-alcohol

Fraction ..	BA	BB	CA	CB
Wt., g.	16·6	7·8	8·9	10·9
I value	1·8	76·5	11·6	96·8

The acid fractions A, BA, BB, CA and CB were separately converted into their methyl esters and then fractionated through an electrically heated and packed column.[1] The analytical details of the various ester-fractions are not recorded in full here, but the final fatty acid composition of each of the three fractions of the fat are summarized in Table II, leading to that of the total fatty acids, together with the probable composition of the glycerides in each of the three fractions and in the whole fat (Table III). The methods of calculation are those described by Hilditch.[2]

Table II

Jaiphal glycerides

Component acids (increments) of glycerides of Jaiphal fats

Fraction	A	B	C	Whole fat
Weight, g.	117·2	31·3	25·6*	174·1
Sap. equiv.	254·4	256·3	275·4	251·8
I value	0·7	25·5	55·1	13·2
Wt.-%	67·32	17·97	14·72	100·0
Mol.-%	69·0	17·6	13·4	100·0
Component acids, mol.-%				
Lauric	—	0·4	—	0·4
Myristic	59·9	10·4	1·5	71·8
Palmitic	8·2	2·4	3·7	14·3
Stearic	—	0·2	1·0	1·2
Tetradecenoic	0·5	0·2	0·1	0·8
Hexadecenoic	0·4	2·5	1·9	4·8
Octadecenoic	—	1·5	3·7	5·2
Octadecadienoic	—	—	1·5	1·5

* Since 13·6 g. of unsaponifiable matter were contained in this fraction which was ultimately removed by extraction, the remainder (25·6 g.) only is taken into account for calculation of component acids and glyceride

A separate determination of fully saturated glycerides was made by the permanganate oxidation method of Hilditch & Lea,[3] the neutral, fully saturated glycerides being recovered by the method of Steger & Von Loon ;[4] 0·20 g. (71·95%) of fully saturated glycerides (I val., nil, acid value, nil) was obtained. As this amount was small, fractionation could not be undertaken.

Discussion

Table III gives the probable glyceride structure of the fat of Jaiphal seeds. It will be seen that the fat contains 71·3% of fully saturated, 20·5% of the disaturated-mono-unsaturated, and 8·2% of the monosaturated-di-unsaturated glycerides. An actual determination of the tri-saturated glyceride content carried out by the method of Hilditch & Lea[3] have a result of 72·7% agreeing well with the calculated figure (71·3%).

Table III

Fraction	*Component glycerides* A	B	C	Whole fat
Component acid groups (increment mol.-%)				
Lauric and myristic	59·9	10·8	1·5	72·2
Palmitic and stearic	8·2	2·6	4·7	15·5
Tetradecenoic and hexadecenoic	0·9	2·7	2·0	5·6
Octadecenoic and octadecadienoic	—	1·5	5·2	6·7
Component glyceride groups (increment mol.-%)				
(*a*) Fully saturated	66·3	5·0	—	71·3
Disaturated mono-unsaturated	2·7	12·6	5·2	20·5
Monosaturated di-unsaturated	—	—	8·2	8·3
(*b*) Trimyristin	41·7	—	—	41·7
Dimyristin mono-others	27·3	13·6	—	40·9
Monomyristin di-others	—	4·0	4·5	8·5
Tri-others	—	—	8·9	8·9
c) Palmitodi-others	24·6	7·2	11·1	42·9
Tri-others	44·40	10·4	2·3	57·1
(*d*) Mono-oleodi-others	—	4·5	11·1	15·6
Tri-others	69·0	13·1	2·3	84·4
Fully saturated glycerides 71·3%				
Trimyristin	41·7	—	—	41·7
Dimyristo-palmitin	24·6	5·0	—	29·6

The fully saturated components may be 41·7% trimyristin and 29·6% dimyristo-palmitin. Earlier results for *Myristica fragrans* seed fat from the East Indies by Collin & Hilditch[5] compare well with those reported here (Indian variety) (see Table IV). Each fat contains, as the

Table IV

Fatty acid components of seed fats of Myristicaceae family

(% of total fatty acids, after allowing for unsaponifiable matter)

Acids	*Myristica fragrans*[5]	*Myristica fragrans* (present work)	*Virola oblobo*[7]	*Myristica malabarica*[8]	*Ucuhuba butter*[9]	*Pycnanthus kombo*[9]
Capric	—	—	—	—	0·5	—
Lauric	1·5	0·4	20·8	—	14·9	5·5
Myristic	76·6	71·8	73·4	39·2	37·2	61·6
Palmitic	10·1	14·3	0·3	13·3	5·0	3·6
Stearic	—	1·2	—	2·4	—	—
Tetradecenoic	—	—	—	—	—	23·6
Hexadecenoic	—	4·8	—	—	—	—
Octadecenoic	10·5	5·2	5·5	44·1	6·4	5·7
Octadecadienoic	1·3	1·5	—	1·0 (and 43·1 resin acid)	—	—

major acid, myristic acid 71·8 and 76·6% of total fatty acids, respectively. The trimyristin content in the present study compares well with the finding of Bomer & Ebach[6] who actually isolated 40% of trimyristin from nutmeg butter.

It is also observed that myristic acid, which is predominant, is distributed in all the glyceride molecules and also occurs twice and thrice in appreciable numbers of the glyceride molecules. The rest of the acyl groups occur only once in some of the glyceride molecules, the number of such molecules depending on the actual proportion of the particular acid in the total mixed fatty acids.

Table V records the actual glyceride groups of the fat as determined by the crystallization technique of the author, the possible glyceride groups calculated according to the rule of even distribution of Hilditch and also the one to be expected from the ' random distribution ' of the acyl radical in the glyceride molecules. It is evident from this table that the acyl radicals are distributed in the nutmeg butter according to the rule of ' even distribution ' of Hilditch. In the earlier study of this seed fat, *Myristica fragrans* by Collin & Hilditch,[5] trimyristin was expected to be 55% in the whole fat according to their ' Association Ratio ' 1·7 to 1 in the saturated-unsaturated glycerides, but it has been shown that the trimyristin content is only 41·7%.

Table V

Glycerides in nutmeg seed fat by crystallization

Glyceride type	Actual	Even	Random
Fully saturated glycerides	71·3	72	67·4
Mono-unsaturated-disaturated glycerides	20·5	20	28·4
Di-unsaturated-mono-unsaturated glycerides	8·2	8	4·0
Tri-unsaturated	—	—	0·2

In other fats of this family (*Myristicaceae*) that have been examined for their glyceride structure, e.g., Virola (*Virola surinamensis*), Kombo (*Pycnanthus kombo*) and *Myristica malabarica*, only the first two have been found to follow the rule of even distribution, the last being an exception to the above rule.[10] This fat appears to be abnormal in more than one respect since it contains nearly 50% of resinous non-fatty matter in addition to glycerides and of the component acids, myristic acid forms only 32%, while there is 17% palmitic and 48% of oleic acid, and the fully saturated glycerides are 16–19%.

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Unsaponifiable matter. Not more than 1 per cent.
Water. Not more than 0.2 per cent.

TESTS

Acid value. Determine as directed under *Method I* in the general procedure, page 748.

Saponification value. Determine as directed in the general method, page 760, using about 3 grams, accurately weighed.

Titer (Solidification Point). Determine as directed under *Solidification Point*, page 787.

Arsenic. A *Sample Solution* prepared as directed for organic compounds meets the requirements of the *Arsenic Test*, page 720.

Heavy metals. Prepare and test a 2-gram sample as directed in *Method II* under the *Heavy Metals Test*, page 763, using 20 mcg. of lead ion (Pb) in the control (*Solution A*).

Iodine value. Determine by the *Wijs Method*, page 752.

Residue on ignition, page 786. Ignite 1 gram as directed in the general method.

Unsaponifiable matter, page 761. Determine as directed in the general method.

Water. Determine by the *Karl Fischer Titrimetric Method*, page 804.

Packaging and storage. Store in well-closed containers.

Functional use in foods. Component in the manufacture of other food grade additives.

MYRISTICA OIL

Nutmeg Oil

DESCRIPTION

The volatile oil obtained by steam distillation from the dried kernels of the ripe seed of *Myristica fragrans* Houttuyn (Fam. *Myristicaceae*). Two types of oil, the East Indian and the West Indian, are commercially available. It is a colorless or pale yellow liquid, having the characteristic odor and taste of nutmeg. It is soluble in alcohol.

SPECIFICATIONS

Angular rotation. *East Indian:* Between +8° and +30°; *West Indian:* Between +25° and +45°.

Refractive index. *East Indian:* Between 1.4740 and 1.4880; *West Indian:* Between 1.4690 and 1.4760 at 20°.

Residue on evaporation. *East Indian:* Not more than 60 mg.; *West Indian:* Not more than 50 mg.

Solubility in alcohol. Passes test.

Specific gravity. *East Indian:* Between 0.880 and 0.910; *West Indian:* Between 0.854 and 0.880.

Limits of Impurities

Arsenic (as As). Not more than 3 parts per million (0.0003 per cent).

Heavy metals (as Pb). Not more than 40 parts per million (0.004 per cent).

Lead. Not more than 10 parts per million (0.001 per cent).

TESTS

Angular rotation. Determine in a 100-mm. tube as directed under *Optical Rotation*, page 780.

Refractive index, page 785. Determine with an Abbé or other refractometer of equal or greater accuracy.

Residue on evaporation. Proceed as directed in the general method, page 746, using 3 ml. of sample, and heat on a steam bath for 5 hours. Then heat at 105° for 1 hour.

Solubility in alcohol. Proceed as directed in the general method, page 746. One ml. of East Indian oil dissolves in 3 ml. of 90 per cent alcohol. One ml. of West Indian oil dissolves in 4 ml. of 90 per cent alcohol.

Specific gravity. Determine by any reliable method (see page 4).

Arsenic. A *Sample Solution* prepared as directed for organic compounds meets the requirements of the *Arsenic Test*, page 720.

Heavy metals. Prepare and test a 500-mg. sample as directed in *Method II* under the *Heavy Metals Test*, page 763, using 20 mcg. of lead ion (Pb) in the control (*Solution A*).

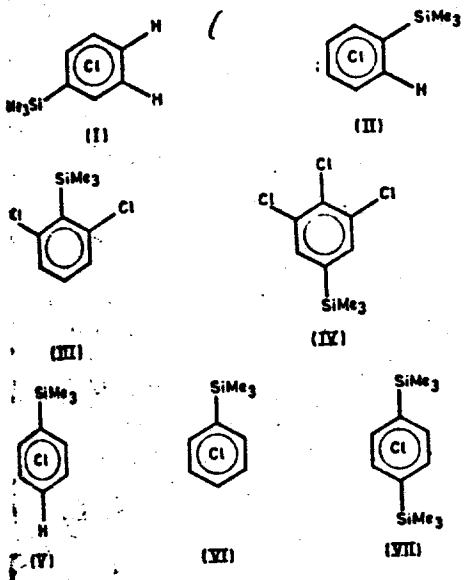
Lead. A *Sample Solution* prepared as directed for organic compounds meets the requirements of the *Lead Limit Test*, page 772, using 10 mcg. of lead ion (Pb) in the control.

Packaging and storage. Store in full, tight containers in a cool place protected from light.

Labeling. Label myristica oil to indicate whether it is the East Indian or West Indian type.

Functional use in foods. Flavoring agent.

In a similar manner, 1,2,3-trichlorobenzene with n-butyllithium undergoes both halogen-metal and hydrogen-metal exchange affording 1,3-dichloro-2-trimethylsilylbenzene (III) and 1,2,3-trichloro-5-trimethylsilylbenzene, (IV), after derivatisation with chlorotrimethylsilane, in the relative proportions indicated in the Table. As in the previous case, *t*-butyllithium reacts preferentially with the chlorine, giving (III) as the only product.



The preference of *t*-BuLi for halogen-metal exchange in its reaction with pentachlorobenzene is less pronounced, although evident. Thus, with this reagent both halogen-metal exchange and hydrogen-metal interconversion occur, to give compounds (V) and (VI) after *in situ* derivatisation with chlorotrimethylsilane, but some (VII) is also formed as a result of a dilithiation; whereas n-butyllithium gives only a hydrogen-metal exchange product (VI) (Table).

The halo-aromatic organolithium compounds formed in the reactions mentioned here are being used for novel syntheses of organosilicon and other organometallic compounds.

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A Wittig reaction of dicarbethoxymethylenetriphenylphosphorane

by D. A. Phipps and G. A. Taylor

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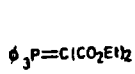
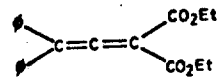
The reactivity of alkylidenetriphenylphosphoranes in the Wittig reaction is associated with the anionic character of the α-carbon atom of the alkylidene group. Substituents at this centre which delocalise the negative charge reduce the reactivity of the phosphorane, and it is normally considered that dicarbethoxymethylenetriphenylphosphorane (I) is inactive in the Wittig reaction on this account. We report now that utilisation of a very reactive carbonyl compound, diphenylketen, brings about a normal Wittig reaction.

Diphenylketen underwent reaction with compound (I) in boiling benzene to give a 30 per cent yield of a compound, $C_{21}H_{20}O_2$, m.p. 102° (from light petroleum), the n.m.r. and infrared spectra ($\nu_{max.}$ (KBr disc) 1937, 1757 cm^{-1}) of which are consistent with the expected product, 1,1-dicarbethoxy-3,3-diphenylpropadiene (II). Although the use of ketens in Wittig reactions has already been described,[1-3] to the best of our knowledge this is the first reported Wittig reaction of compound (I).



(I)



(II)

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Identification of the major components of nutmeg oil by gas chromatography and mass spectrometry

by G. M. Sammy and W. W. Nawar*

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In our investigation of the volatile components from the oil of Nutmeg (*Myristica fragrans*), ten monoterpene hydrocarbons, six monoterpene alcohols, one sesquiterpene and five aromatic ethers were identified (see Table). In addition, six gas chromatographic peaks with a molecular ion of *m/e* 154, seven peaks with a molecular ion of *m/e* 204 and one with a molecular ion of *m/e* 136 were present but were not positively identified.

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Table
Volatile compounds identified in nutmeg oil

Hydrocarbons (Monoterpene)	*Molecular weight*
α-Pinene	136
Camphene	136
β-Pinene	136
α-Phellandrene	136
Myrcene	136
α-Terpinene	136
p-Cymene	136
Terpinolene	136
Alcohols (Monoterpene)	
Linalool	154
4-Terpineol	154
α-Terpineol	154
Citronellol	156
β-Terpineol	154
Geraniol	154
Sesquiterpene	
β-Caryophyllene	204
Aromatic ethers	
Safrole	162
Methyl eugenol	178
Myristicin	192
cis-iso-Elemicin[a]	208
Trans-iso-Elemicin[a]	208

[a] tentative

The occurrence of methyl eugenol in nutmeg oil was previously suspected[1,2] but never proved. This compound gives a mass spectrum similar to that of methyl isoeugenol except for the peak at M-27 which is present for methyl eugenol but not for methyl isoeugenol. Methyl eugenol has an allylic side chain and fission at the α-β carbon-carbon bond gives the M-27 fragment. Methyl isoeugenol, on the other hand, has a propenylic side chain which is in conjugation with the benzene ring and, therefore, rupture at the above site is unlikely.

Since an authentic sample of isoelimicin was not available, its identification was considered tentative. This was based on a study of its mass spectrometric fragmentation pattern (Fig.) as compared with isoeugenol and methyl isoeugenol. Only the prominent peaks above *m/e* 50 are shown in the Fig. Each of the two gas chromatographic peaks assigned the structure isoelimicin gave a strong molecular ion at *m/e* 208, a strong M-15 peak, a moderate M-31 peak and no significant peak at M-27. Both peaks had identical spectra suggesting they could be the *cis-trans* isomers.

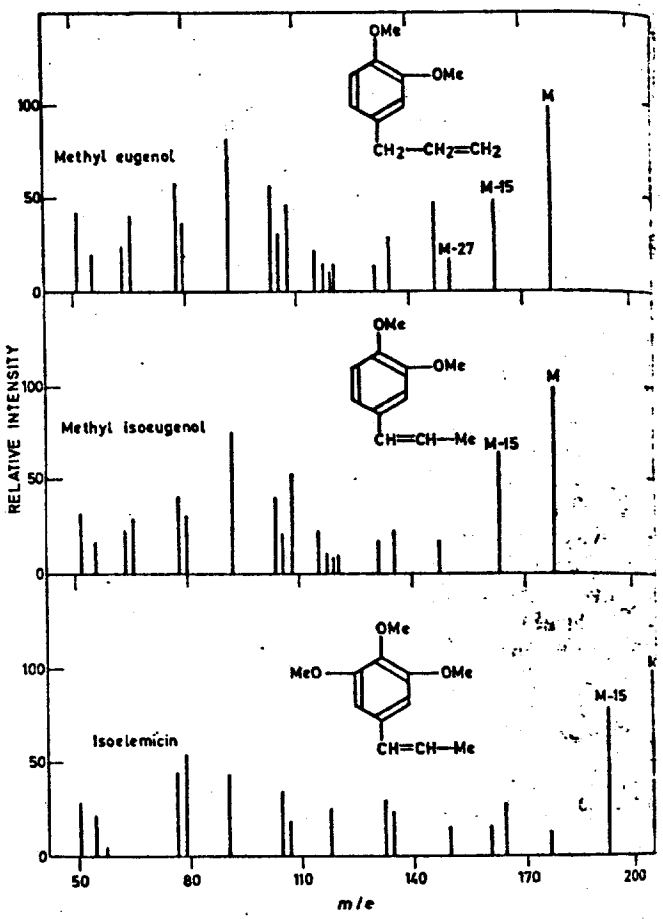
Analysis of the nutmeg fat gave the following fatty acid composition:

Fatty acid	*Carbon no.*	*Per cent of total fatty acids*
Lauric	12	2·0
Tridecanoic	13	0·7
Myristic	14	90·4
Pentadecanoic	15	0·2
Palmitic	16	2·2
Heptadecanoic	17	0·2
Stearic	18	0·4
Oleic	18:1	3·9

The nutmeg oil was obtained from Grenada nutmeg by steam-distillation, and separated into fractions by column chromatography on silica-gel. Fourteen fractions were obtained by eluting successively with light petroleum, cyclohexane, benzene, acetone and finally with ethyl alcohol.

Gas chromatographic analysis was conducted on tw capillary columns (*i.e.* Carbowax 20M and diethylene glyc succinate polyester) and a ½th in column packed wit silicone rubber SE30. The effluent from each gas chromato graphic column was admitted through a heated line to helium separator and then to the ion source of an Hitachi Perkin-Elmer RMU-6A mass spectrometer. The ion sour was equipped with a total ion monitor. A compound w accepted as fully characterised only when it met tw requirements. First, its gas chromatographic retention mus agree with that of an authentic sample on three differen columns. Second, the mass spectra of the compou separated from the three columns must agree with each other and with that of the authentic sample.

Determination of the fatty acid composition was done by inter-esterification[3] followed by analysis of the methyl esters by gas chromatography and mass spectrometry.



We thank Professor Hiroshi Mitsuhashi of the University of Hokkaido, Japan, for supplying the sample of Myristicin, the Grenada Nutmeg Association for providing the nutmeg and U.N.E.S.C.O. for providing a fellowship to G.M.S. which made this study possible.

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Report on Volatile Oil in Spices

By N. AUBREY CARSON, *Associate Referee* (Food and Drug Administration, Department of Health, Education, and Welfare, St. Louis 1, Mo.)

In 1957 direct stirring devices were compared with magnetic stirring devices for determination of volatile oil in spices (1). No adequate seal was found for direct stirring that gave as high volatile oil content or as precise results as magnetic stirring. Subcommittee C recommended that a collaborative study be made of the modified method (2).

Three prepared spices were sent to eight collaborators. A lighter-than-water trap with added xylene was used for all three determinations. Collaborators were directed to place samples in a freezer upon receipt. They were also instructed to cool the distillate, read the volume of collected oil the same day of distillation, keep the condenser water running all night, and read again the next morning.

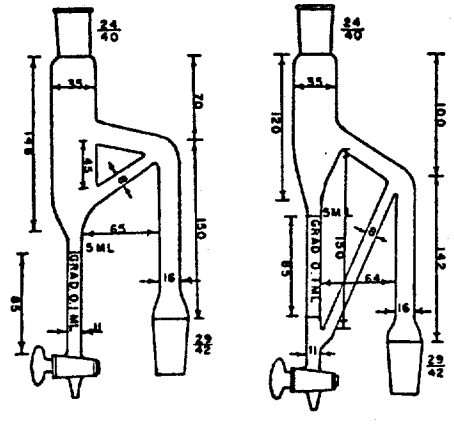
The following method was used:

METHOD

Apparatus

(a) *Volatile oil traps.*—Clevenger type, modified, with ⅎ ground joints; (1) lighter-than-water design for oils with densities near or less than that of water; (2) heavier-than-water design for oils with densities greater than water.

(b) *Magnetic stirring apparatus.*—Heavy duty; with egg-shaped magnetic stirring bar or other suitable bar.



HEAVIER THAN WATER LIGHTER THAN WATER

(c) *Flask.*—Round-bottom, short-neck, 1 L size, with ⅎ glass joint.

Determination

Prepare sample as in 28.1, except use No. 20 sieve.

Transfer enough weighed sample to 1 L flask to yield 2–4 ml volatile oil. Add water to fill flask half full. Insert stirring bar and place flask in heating mantle set over magnetic stirrer. Use piece of antifoam agent, such as Dow Corning Antifoam Emulsion, about size of pea. Fill trap with water; to lighter-than-water trap add 1 ml of xylene, accurately measured; omit xylene from heavier-than-water trap or if volatile oil is needed subsequently for identification tests and oil does not separate in trap. Clean trap just before use. Set up apparatus so condensate will not drop directly on surface of liquid in trap but instead will run down side, and stir suspension with magnetic stirrer. Set heating mantle transformer at 90 volts (not over 3 amperes).

If oil separates in graduated portion of trap or clings to walls, add several drops of saturated aqueous detergent solution through the top of the condenser. Repeat, if necessary (usually once is enough). Distill 10 minutes after adding the detergent so as to wash it out of the trap.

Distill until two consecutive readings taken at 1 hour intervals show no change in oil content (not less than 6 hours). Cool and read the volume of collected oil. Subtract the amount of xylene added and report oil as ml/100 g spice.

Results

Results are given in Table 1.

Despite the fact that very few collaborators had any previous experience with the apparatus or the method, the interlaboratory standard deviations were very low. The precision of the individual analysts was much greater than that between laboratories. This was to be expected with different apparatus. The results of Collaborator 7 were not used in calculating the standard deviation because he did not follow the method as directed.

Volatile oils of nutmeg and allspice take

Table 1. Collaborative results for volatile oil in spices

Coll.	Nutmeg, % of Oil Same Day	Nutmeg, % of Oil Next Day	Caraway, % of Oil Same Day	Caraway, % of Oil Next Day	Allspice, % of Oil Same Day	Allspice, % of Oil Next Day
1	10.80	10.48	4.56	4.40	3.13	3.13
	10.80	10.56	4.66	4.52	3.20	3.20
	10.88	10.72	4.60	4.48	3.33	3.20
					3.20	3.16
					3.20	3.07
2	10.96	10.80	4.74	4.54	3.24	3.07
	11.12	10.80	4.70	4.50	3.24	3.12
3	11.00	10.88	4.80	4.76	3.01	3.00
	10.92	10.88	4.82	4.78	3.04	3.03
	10.84	10.80	4.80	4.76	3.03	3.03
	10.88	10.80	4.82	4.74	3.03	3.04
4	10.80	10.64	4.44	4.40	3.20	3.09
	10.88	10.80	4.56	4.52	3.20	3.17
5	11.00	11.00	4.60	4.56	3.13	3.13
	11.12	11.12	4.66	4.60	3.20	3.17
6	11.00	10.80	4.50	4.40	3.20	3.20
	10.40	10.40	4.60	4.50	3.20	3.20
7[a]	10.72	10.92	4.50	4.48	2.92	2.84
	10.16	9.96	4.26	4.30	3.05	2.98
8	11.68	11.28	4.96	4.86	3.25	3.16
	11.60	11.28	5.00	4.88	3.24	3.15
Av.	10.99	10.84	4.70	4.60	3.17	3.12
Std. Dev.	±0.33	±0.24	±0.16	±0.16	±0.09	±0.07
	3.01%	2.22%	3.41%	3.48%	2.84%	2.24%

[a] Collaborator 7's results were not used in calculating the average or standard deviation.

longer to clear than caraway. Thus the standard deviation for nutmeg and allspice when read the same day as distilled was higher than when read next day. Standard deviation for caraway was lower when read the same day than when read the next day.

All collaborators made determinations in the latter part of May or the early part of June except No. 8 who did not have apparatus available until the middle of July.

Xylene was added to the volatile oils of all three spices by the collaborators. The addition of xylene proved of value for those volatile oils which ordinarily separate in the lighter-than-water trap. But xylene did not significantly improve the accuracy of the method for caraway.

Summary and Recommendations

A collaborative study was made of commercially ground nutmeg, allspice, and caraway. These spices have been difficult to analyze for volatile oil content in the past. Ground glass connections, electric heating mantles, and magnetic stirring devices were used in this study. Xylene was added to traps in all cases. The standard deviation varied from 2.24 to 3.48%.

This new apparatus and method have not been tested extensively against spices of low volatile oil content. For such spices, a modified Clevenger trap with smaller bore graduations or Lee and Ogg's trap (3) may be advisable.

It is recommended*—

(1) That the method submitted this year be further revised as follows, and that the revised method be adopted as first action:

(*a*) In the second paragraph, delete, beginning: "to lighter-than-water trap add 1 ml of xylene . . ." through "does not separate in trap." When the density of volatile oil is nearly one, as in cassia, or the oil contains two fractions that separate in the trap, as

* For report of Subcommittee C and action of the Association, see *This Journal*, 42, 25, 26 (1959).

in nutmeg and allspice, 1 ml of xylene, accurately measured, should be added to the lighter-than-water trap.

(*b*) Change the last sentence of the last paragraph to read: "If xylene was added, subtract 1.00, and report oil as ml/100 g spice."

(2) That further work be done on spices of low volatile oil content by the proposed method.

Acknowledgments

The author wishes to thank Clyde L. Ogg, head of the Eastern Regional Research Laboratory, Department of Agriculture, for his many contributions and valuable advice, and P. R. Dotts of the same laboratory for his collaborative work. The author also wishes to thank the following collaborators, all of the Food and Drug Administration: H. D. Silverberg, St. Louis; G. R. Reed, Cincinnati; T. S. Smith, Kansas City; F. B. Jones, New York; L. G. Ensminger, Los Angeles, and F. A. Leal, New Orleans.

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Report on Sugar, Ash, and Pungent Principles in Mustard

By ALDRICH F. RATAY, *Associate Referee* (Food and Drug Administration, Department of Health, Education, and Welfare, Philadelphia 6, Pa.)

The present study was undertaken on the recommendation of Subcommittee C and under the direction of the Referee on Spices and Other Condiments.

No work was done on pungent principles.

Sugar in Mustard.—In the previous work on sugar in prepared mustard, the Associate Referee obtained high recoveries by methods 22.34 and 22.35 (*This Journal*, 41, 253 (1958)). Substituting ion exchange resins for lead acetate to clarify the product made little or no improvement. This year an effort was made to find the causes of high recovery.

Methods 22.34 and 22.35 were used to check the recovery of pure sucrose alone. No clarifiers were used and the sugar solutions were inverted with invertase. Excellent results were obtained.

In determining sugar in mustard, the Associate Referee tried several modifications: eliminating, increasing, or reducing the amount of basic material used for neutralization at the beginning, substituting invertase for hydrochloric acid during inversion, and eliminating the use of a clarifier. None of these changes revealed the factors causing high sucrose recoveries. However, some improvement was noted when the mustard solution (with added sucrose) was cooled after being heated on the steam bath, diluted to volume, allowed to stand about 18 hours, and then centrifuged for 10 minutes at 1200 rpm, with the clarifiers eliminated. Recoveries of sucrose were reduced to 103% (a 2% reduction); that is, 515 mg of sucrose was recovered for each 500 mg of sucrose added.

Ash in Mustard.—Prepared mustard was selected for the original work. Experimental analyses disclosed that the method for solids, 28.30, was applicable. The following method was worked out:

Weigh a 5 gram sample into a flat-bottom platinum dish, and distribute it evenly over the bottom with a little water. Evaporate to dryness on a water or steam bath, and ignite in the muffle 60 minutes at 550°. Break up the charred mass with a small amount of water, evaporate as before, and ignite again until a light gray ash is formed,

magnetic stirring. The vigorous evolution of trimethylamine gas from the reaction mixture was observed during the early part of the reaction. The reaction mixture was then brought to dryness under reduced pressure. The dried residue was triturated with 50 ml. of water and 200 ml. of ether. The aqueous layer was washed with 100 ml. of ether. The ethereal layer was combined with the washing, washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness to leave a 0.75-Gm. yellow oil. The des-*N*-methine crystallized from ether as colorless fine prisms (0.64 Gm.), m.p. 170–172°, $[\alpha]_D^{25} \pm 0°$ (c 2.05, chloroform); $\lambda_{max.}$ 267 mμ (ε 55,000), 317 mμ (ε 31,000); N.M.R. spectrum ($CDCl_3$), τ = 5.76, 5.83, 5.88, 5.91, 6.05, 6.07, 6.19 (21H, O-methyl).

Anal.—Calcd. for $C_{33}H_{38}O_8$: C, 73.80; H, 6.04. Found: C, 73.54; H, 6.20.

PHARMACOLOGICAL RESULTS[3]

Thalicarpine was evaluated in a variety of pharmacologic procedures and found to possess a modicum of biological activity. In acute dose range or toxicity studies, oral doses of 300 mg./Kg. failed to produce discernible gross behavioral changes in the mouse. Intraperitoneal injection of 25 mg./Kg. of thalicarpine to a cat produced sensitivity of the forepaws, rubbing of the neck, and emesis.

The principal action of thalicarpine on blood pressure was depressor in nature. In the cat anesthetized with chloralose, mean arterial blood pressure was lowered transiently following acute intravenous doses ranging from 0.5 to 5 mg./Kg. Lethality, due to respiratory arrest, occurred at a dose of 10 mg./Kg. Bradycardia, respiratory depression, and andrenergic blocking action accounted for the weak hypotensive activity. Anticoagulant, hypoglycemic, and anticonvulsant properties were not observed after oral doses of 100 mg./Kg. in the rat, guinea pig, or mouse, respectively. An oral dose of 50 mg./Kg. caused a slight antidiuretic response in rats hydrated with saline. In the Randall and Selitto test for anti-inflammatory activity oral doses of 50 mg./Kg. of thalicarpine produced a very low order of analgetic activity (25%) and no significant antipyretic action.

In summary, weak hypotensive activity of a transient nature was the principal action of thalicarpine when injected intravenously into the anesthetized cat. Respiratory toxicity and weak adrenolytic activity accompanied this action. Thalicarpine failed to exhibit significant biological activity as an anti-inflammatory, anticoagulant, hypoglycemic, or diuretic agent.

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Gas Chromatographic Analysis of Oil of Nutmeg

By ELWINA A. BEJNAROWICZ and ERNST R. KIRCH

Four samples of commercially available oil of nutmeg were analyzed by gas chromatography. Of a number of stationary liquid phases used, a 20 per cent Reoplex 400 on Dichromite gave the best separation. The composition of the oils was determined on the basis of retention times and enrichment.

ESSENTIAL OILS contain volatile compounds representing many classes of organic substances. One such volatile oil is the well known oil of nutmeg (*Myristica*), an important spice used for the flavoring of numerous food products. It is also used as a component of certain types of perfumes and as a flavoring agent for dentifrices (1). The literature lists two oils of myristica—oil of nutmeg and oil of mace. Both are derived from the fruit of *Myristica fragrans* Houtt. (*fam. Myristicaceae*) (2).

The dried seeds of nutmeg contain from 5 to 15% of the volatile oil, as well as from 25 to 40% of a fixed oil, and from 5 to 15% of ash. The rest consists of moisture, fiber, and starch (3, 4).

There are two principal types of nutmeg which are recognized today, and these depend primarily on geographical origin. "Banda nutmegs" or East Indian variety are the finest; the other variety comes from the West Indies (5).

The West Indian type of oil has a lower specific gravity, lower refractive index, and a lower residue on evaporation, but has a higher

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optical rotation than the oil obtained from the East Indies.

Nutmeg oil consists principally of terpenes, and about 60% of the oil distils below 180° (6). In 1907, Power and Salway (7) examined a "genuine" oil of Ceylon nutmeg having a specific gravity of 0.8690 at 15° and an optical rotation of 38°4′. They found this oil to contain primarily over 80% of terpenes and 6% terpene alcohols.

In reviewing the literature concerning differences between East Indian and West Indian oil, one finds statements primarily referring to the higher content of terpenes and a lower content of phenols in the West Indian oil. Therefore, it was of interest to undertake an analysis of the nutmeg oil obtained from these two sources, using gas chromatography.

EXPERIMENTAL

Apparatus.—The apparatus employed was Beckman GC-2 gas chromatograph with a four-filament thermal conductivity cell connected to Sargent SR recorder equipped with a K-4 disk integrator. Helium was used as the carrier gas, and the flow rate was maintained at 38 ml. per minute. The filament current used was 380 ma., while the chart speed of the recorder was 1.0 in. per minute.

Column Preparation.—Reoplex 400 (polyethylene glycol adipate) was used as the stationary liquid phase and was supported on 80/100-mesh Diachromite. Approximately 20.0 Gm. of the solid support was required to pack a 6-ft. column. The 5-Gm. liquid phase was introduced by deposition gradually and with constant stirring from a 45 ml. solution in dichloromethane. The resulting mixture was first dried in air, then at 90° in the oven for about 3 hours. Columns used were of copper tubing, 1/4 in. diam. and 6 ft. in length.

Operating Conditions.—Temperatures ranging from 100 to 190° were employed. Samples of 0.005 ml. were used, except in cases where the fraction was collected. Then the sample was increased to 0.05 ml.

Oil Samples and Standard Compounds.—The four commercially available samples of nutmeg oil that were analyzed are listed below along with their respective specific gravities and refractive indices.[1] Sample A (East Indian nutmeg oil U.S.P. extra) n_D^{20}, 1.4804; sp. gr.^{24}, 0.884. Sample B (East Indian nutmeg oil U.S.P.) n_D^{20}, 1.4809; sp. gr.^{24}, 0.897. Sample C (East Indian nutmeg oil U.S.P.) n_D^{20}, 1.4793; sp. gr.^{24}, 0.880. Sample D (West Indian nutmeg oil U.S.P.) n_D^{20}, 1.4756; sp. gr.^{24}, 0.870.

For purposes of identification the retention times and relative retention times of the unknown were compared with a known pure standard sample. In this way a tentative identification of most of the compounds could be made. We have confirmed these particular results by enrichment method, in which known compounds were added individually to the sample chromatographed and compared in each instance to the chromatogram obtained by using the oil alone. Infrared spectra were obtained for unknown peaks. Tables I, II, and III list the retention times and relative retention times of standard compounds at 100 and 160°, respectively. Relative retention times are based on *p*-cymene.

[1] The authors express their thanks to Fritzsche Brothers, Inc., New York, N. Y., for supplying Sample C of oil of nutmeg.

TABLE I.—RETENTION TIMES AND RELATIVE RETENTION TIMES OF STANDARD COMPOUNDS ON REOPLEX 400 AT 100°C. (FLOW RATE, 38 ML./MIN.; FILAMENT CURRENT, 380 MA.; *p*-CYMENE = 1.00)

Standard Compd.	Retention Times, min.	Relative Retention Times
dl-α-Pinene	3.36	0.25
d-Camphene	4.56	0.34
β-Pinene	5.56	0.41
Terpinolene	7.56	0.56
d-Limonene	8.80	0.65
p-Cymene	13.5	1.00
dl-Linalool	52.4	3.88
Camphor	54.0	3.99
dl-α-Terpineol	129	9.51

TABLE II.—RETENTION TIMES AND RELATIVE RETENTION TIMES OF STANDARD COMPOUNDS ON REOPLEX 400 AT 130°C. (FLOW RATE, 38 ML./MIN.; FILAMENT CURRENT, 380 MA.; *p*-CYMENE = 1.00)

Standard Compd.	Retention Times, min.	Relative Retention Times
dl-α-Pinene	1.89	0.33
d-Camphene	1.95	0.34
β-Pinene	3.02	0.51
Terpinolene	3.69	0.65
d-Limonene	4.24	0.72
p-Cymene	5.70	1.00
dl-Linalool	16.6	2.90
Camphor	19.2	3.37
dl-Borneol	28.9	5.06
dl-α-Terpineol	34.7	6.09
Geraniol	67.3	11.8
Safrole	80.7	14.2
Eugenol (was not eluted even after 125 min.)		

TABLE III.—RETENTION TIMES AND RELATIVE RETENTION TIMES OF STANDARD COMPOUNDS ON REOPLEX 400 AT 160°C. (FLOW RATE, 38 ML./MIN.; FILAMENT CURRENT = 380 MA.; *p*-CYMENE = 1.00)

Standard Compd.	Retention Times, min.	Relative Retention Times
dl-α-Pinene	1.32	0.42
d-Camphene	1.32	0.42
β-Pinene	1.88	0.59
Terpinolene	2.22	0.70
Limonene	2.44	0.78
p-Cymene	3.18	1.00
dl-Linalool	7.00	2.20
Camphor	9.53	3.00
dl-α-Terpineol	14.6	4.58
Geraniol	24.9	7.55
Safrole	30.5	9.62
Eugenol	83.0	26.1
Isoeugenol	146	46.1

RESULTS AND DISCUSSION

Three commercial samples of an East Indian nutmeg oil and one sample of a West Indian nutmeg oil were analyzed by gas liquid partition chromatography. Of a number of stationary liquid phases that were used, only Reoplex 400 supported on 80/100-mesh Dichromite gave satisfactory results.

That the various components of the nutmeg oils could be separated more efficiently at different temperatures is shown in Figs. 1–3 when Sample A of oil of nutmeg was chromatographed at 100, 130, and 160°, respectively. For example, eight peaks were observed at 100° (Fig. 1), while at 130° the number of peaks increased to ten (Fig. 2). At 160°, two additional peaks were obtained using this same oil (Fig. 3). Similar results were observed with the other samples of the East Indian variety oil.

Attention should be directed to Fig. 2 which shows ten peaks obtained with Sample A at 130°. Comparing this with the chromatograms representing the peaks obtained at 100° (Fig. 1) and 160° (Fig. 3), respectively—and using this same oil—it should be pointed out that in the chromatogram obtained at 100°, peak numbers 8, 9, 10, 11, and 12 (Fig. 3), representing higher retention times, are absent. It was further observed that peak number 3 at 130° (Fig. 2) or 160° (Fig. 3) could be resolved into two components at 100°. One of these peaks (No. 3) we have identified as limonene.

We have used the results obtained at 100 and 160°, respectively, to calculate the percentages of the components of the East Indian oils (Samples A, B, and C). With the West Indian oil (Sample D) two unidentified components which appeared as two distinct small peaks at 130° (Fig. 5) but only as one peak at 160° (Fig. 6) were observed. At temperature of 100° (Fig. 4) these same constituents also appeared as two peaks, but one of them (with the lower retention time) could not be separated distinctly from the preceding one. The results obtained at 130° were also used to calculate the percentages of these two components of the oil. We have based all the percentages as calculated on the total eluted. To keep the peaks within the limits, it is customary to change attenuation at times from component to component. This was done in this investigation also. It is well recognized, however, that a particular area will differ with change in attenuation. Since the percentages are calculated from the integrated signals, and since these signals are proportional to the attenuation, each sample of the oil was re-run at one and the same attenuation.

The samples of the East Indian oil of nutmeg (Samples A, B, and C) that were examined differed in composition not only from the West Indian oil, but they also showed variation in composition from one to the other (Table IV).

All of the oils of the East as well as the West Indian variety were found to contain α-pinene, β-pinene, and limonene. Of the four samples of oil that we have investigated, the West Indian variety contained the highest total percentage (40.1%) of these terpenes, while the East Indian Samples A, B, and C contained 30.9, 30.2, and 33.9-

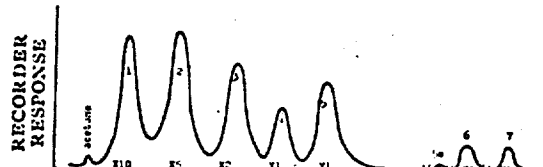

Fig. 1.—Typical chromatogram of Sample A of nutmeg oil on Reoplex 400 at 100°C.

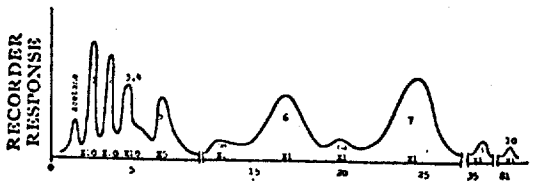

Fig. 2.—Typical chromatogram of Sample A of nutmeg oil on Reoplex 400 at 130°C.

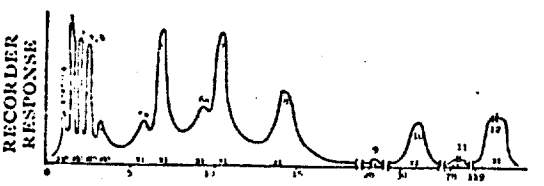

Fig. 3.—Typical chromatogram of Sample A of nutmeg oil on Reoplex 400 at 160°C.

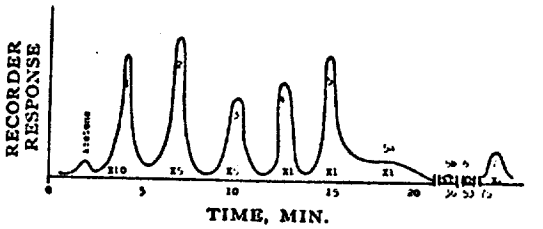

Fig. 4.—Typical chromatogram of Sample D of nutmeg oil on Reoplex 400 at 100°C.

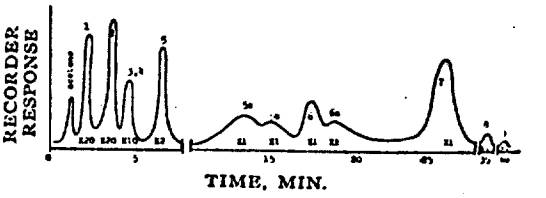

Fig. 5.—Typical chromatogram of Sample D of nutmeg oil on Reoplex 400 at 130°C.

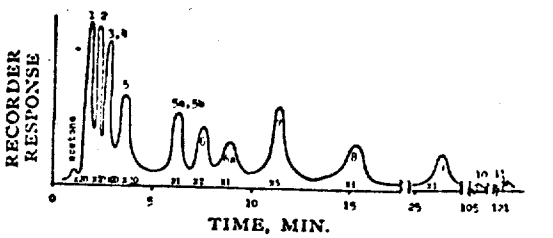

Fig. 6.—Typical chromatogram of Sample D of nutmeg oil on Reoplex 400 at 160°C.

TABLE IV.—COMPOSITION OF NUTMEG OILS, PER CENT

	Sample A	Sample B	Sample C	Sample D
α-Pinene	13.9	12.9	12.5	13.4
β-Pinene	12.3	12.6	19.1	14.8
Terpinolene	...	1.4	0.8	...
Limonene	4.7	4.7	2.3	11.9
p-Cymene	1.6	2.6	2.7	4.3
Linalool	10.6	8.1	...	5.9
Camphor	...	...	...	3.4
Terpinen-4-ol	14.5	14.2	19.5	24.7
α-Terpineol	7.7	4.7	4.0	5.0
Geraniol	0.3	11.9	...	3.6
Safrole	6.0	4.2	5.5	...
Eugenol	1.3	3.8	0.3	...
Unknown A	22.2	13.9	25.9	1.7
Unid. (3 components)	4.9	5.4	...	...
Unid. (4 components)	...	...	7.4	11.4

%, respectively. Table IV lists the percentages of individual components in each of the oils. The presence of terpinolene was observed only in Samples B and C and in 1.4 and 0.8%, respectively. One of the peaks which appeared on each of the chromatograms was identified as p-cymene and ranged from 1.6 to 4.3% (Table IV).

It should be noted that linalool and geraniol are absent in Sample C of the East Indian nutmeg oil. Samples A, B, and D contain linalool in 10.6, 8.1, and 5.9%, respectively. Geraniol was found to be present in two samples of the East Indian oil, Samples A and B. It is interesting that there is a large difference in percentage of geraniol in the two oils—namely, 0.3% in Sample A and 11.9% in Sample B. In the West Indian oil, 3.6% geraniol was found.

A component with relative retention times ranging from 5.48 to 5.58 at 100°, 4.15 to 4.31 at 130°, and 3.22 to 3.26 at 160° (Tables V, VI, VII, and VIII) which was present in all the oils, was collected and an infrared spectrum was obtained. By comparison of I.R. spectra, this compound is tentatively identified as terpinen-4 ol. West Indian nutmeg oil contained the highest amount of terpinen-4 ol (24.7%), while East Indian oils as analyzed contained the following percentages of this alcohol: 14.5, 14.2, and 19.5% for Samples A, B, and C, respectively. As can be seen from Figs. 2 and 5, another component is present with a higher retention time (peak 8). This is present in approximate range of 4–8%, depending upon the oil; it has been tentatively identified as α-terpineol using the enrichment procedure.

While safrole and eugenol were absent in the West Indian oil, both of these were present in all three samples of the East Indian variety. The per cent of safrole ranges from 4.2 to 6.0 and that of eugenol from 0.3 to as high as 3.8% (Table IV).

Another component (Unknown A) found in all samples of oil tested had a relative retention time ranging from 37.3 to 38.6 (Tables V, VI, VII, and VIII) at 160°. It was collected and its infrared

TABLE V.—RELATIVE RETENTION TIMES OF SAMPLE A OF EAST INDIAN NUTMEG OIL. (STATIONARY PHASE-REOPLEX 400; HELIUM FLOW RATE 38 ML./MIN. p-CYMENE = 1.00; FIGS. 1, 2, AND 3)

Peak No., Compd.	100°C. Unknown	100°C. Known	130°C. Unknown	130°C. Known	160°C. Unknown	160°C. Known
1. α-Pinene	0.25	0.25	0.32	0.33	0.42	0.42
2. β-Pinene	0.42	0.41	0.50	0.51	0.60	0.59
3. Limonene	0.66	0.65	0.71	0.72	0.78	0.78
4. Unidentified	0.86	...	...	...	...	...
5. p-Cymene	1.00	1.00	1.02	1.00	0.99	1.00
5a. Unidentified	2.67	...	2.04	...	1.82	...
6. Linalool	3.88	3.88	2.86	2.90	2.16	2.20
6a. Unidentified	...	...	3.49	...	2.74	...
7. Terpinen-4-ol	5.55	...	4.15	...	3.22	...
8. α-Terpineol	...	...	6.10	6.09	4.45	4.58
9. Geraniol	...	...	...	...	8.00	7.55
10. Safrole	...	...	14.2	14.2	9.24	9.62
11. Eugenol	...	...	...	...	22.5	26.1
12. Unknown A	...	...	...	...	37.3	...

TABLE VI.—RELATIVE RETENTION TIMES OF SAMPLE B OF EAST INDIAN NUTMEG OIL. (STATIONARY PHASE-REOPLEX 400; HELIUM FLOW RATE 38 ML./MIN. p-CYMENE = 1.00)

Peak No., Compd.	100°C. Unknown	100°C. Known	130°C. Unknown	130°C. Known	160°C. Unknown	160°C. Known
1. α-Pinene	0.24	0.25	0.33	0.34	0.41	0.42
2. β-Pinene	0.42	0.41	0.53	0.51	0.59	0.59
2a. Terpinolene	0.60	0.56	...	...	...	...
3. Limonene	0.64	0.65	0.75	0.72	0.79	0.78
4. Unidentified	0.84	...	...	...	...	...
5. p-Cymene	1.00	1.00	1.06	1.00	1.05	1.00
5a. Unidentified	2.68	...	2.08	...	1.86	...
6. Linalool	3.79	3.88	2.88	2.90	2.20	2.20
6a. Unidentified	...	...	3.55	...	2.80	...
7. Terpinen-4-ol	5.48	...	4.22	...	3.23	...
8. α-Terpineol	...	...	6.18	6.09	4.41	4.58
9. Geraniol	...	...	11.9	11.8	7.79	7.55
10. Safrole	...	...	14.3	14.2	9.53	9.62
11. Eugenol	...	...	...	...	24.2	26.1
12. Unknown A	...	...	...	...	38.6	...

spectrum was obtained. The spectrum showed absorption bands usually associated with aromatic ring, 1630 cm.$^{-1}$, 1516 cm.$^{-1}$, 1459 cm.$^{-1}$, and a carbonyl group 1718 cm.$^{-1}$ The quantity of this component ranged from a low of 1.7% in the West Indian oil to a high of 25.9% in Samples C of East Indian variety (Table IV).

Results obtained by the authors differ from those reported for the oil of nutmeg not only qualitatively but also quantitatively, with the possible exception of trace amounts of the esters of fatty acids, which we did not observe under the conditions used. Myristic acid and myristicin which have been reported present in a concentration of 2–3% were not eluted even after 105 minutes at a higher temperature (190°) than that used for the final analysis of the other components of the oils.

In most instances Power and Salway (8) listed the combined percentages of a few components. For example, according to these investigators α-pinene and *d*-camphene make up about 80% of the oil. Others have reported the presence of about 70% of terpenes (α-pinene, *d*-camphene, β-pinene, and dipentene). Analysis of the four samples of oil examined by us confirmed the presence of α-pinene. Samples A, B, C, and D were observed to contain 13.9, 12.9, 12.5, and 13.4% of α-pinene, respectively, while *d*-camphene was not present.

Only a small amount of β-pinene was detected in an oil analyzed in another study (9). The percentages of β-pinene observed in the present study differ considerably. As can be seen from Table IV, the percentage of β-pinene varies from a low of 12.3% to a high of 19.1%.

About 8% of a substance called dipentene was reported present in the oil analyzed by Power and Salway. It is important to note that this substance identified as dipentene by them (8) is not a pure compound but rather a mixture composed of $C_{10}H_{16}$ terpenes. Westaway and Williams (10) have analyzed two synthetic and two natural samples labeled as dipentene. Both types of samples differed both qualitatively and quantitatively. One natural sample contained as high as 80% of limonene; in the other three samples, limonene was present in various lower concentrations. Terpinolene was observed in varying percentages in all four samples. Other terpenes which were reported present by Westaway and Williams in some samples and absent in others include α-pinene, *d*-camphene, β-pinene, tricyclene, α- and γ-terpinene.

A peak labeled number three (Fig. 1) in this study present in each of the four oils and identified as limonene is the main component of dipentene referred to by Power and Salway. Furthermore, Samples B and C contained small amounts of terpinolene which were not reported present in the oil of nutmeg.

Power and Salway (9) identified *d*-linalool, *d*-borneol, "isoterpineol," and geraniol in nutmeg oil. They reported these four alcohols present in about a total of 6%. In this investigation borneol was absent in all samples of nutmeg oil, while another

TABLE VII.—RELATIVE RETENTION TIMES OF SAMPLE C OF EAST INDIAN NUTMEG OIL. STATIONARY PHASE-REOPLEX 400; HELIUM FLOW RATE 38 ML./MIN. *p*-CYMENE = 1.00

Peak No., Compd.	100°C.		130°C.		160°C.	
	Unknown	Known	Unknown	Known	Unknown	Known
1. α-Pinene	0.23	0.25	0.35	0.34	0.42	0.42
2. β-Pinene	0.41	0.41	0.54	0.51	0.59	0.59
2a. Terpinolene	0.63	0.56	...	...	...	...
3. Limonene	0.70	0.65	0.74	0.72	0.80	0.78
4. Unidentified	0.86	...	...	...	...	...
5. *p*-Cymene	1.02	1.00	1.03	1.00	1.07	1.00
6. Unidentified	...	...	2.12	...	1.30	...
6a. Unidentified	...	...	2.61	...	2.14	...
6b. Unidentified	...	...	3.04	...	2.57	...
7. Terpinen-4-ol	5.58	...	4.31	...	3.26	...
8. α-Terpineol	...	...	6.45	6.09	4.56	4.58
9. Safrole	...	...	14.7	14.2	9.53	9.68
10. Eugenol	...	...	...	...	24.3	26.1
11. Unknown A	...	...	...	...	38.6	...

TABLE VIII.—RELATIVE RETENTION TIMES OF SAMPLE D OF WEST INDIAN NUTMEG OIL, (STATIONARY PHASE-REOPLEX 400; HELIUM FLOW RATE 38 ML./MIN. *p*-CYMENE = 1.00; FIGS. 4, 5, AND 6)

Peak No., Compd.	100°C.		130°C.		160°C.	
	Unknown	Known	Unknown	Known	Unknown	Known
1. α-Pinene	0.24	0.25	0.32	0.33	0.42	0.42
2. β-Pinene	0.43	0.41	0.53	0.51	0.59	0.59
3. Limonene	0.66	0.65	0.72	0.72	0.78	0.78
4. Unidentified	0.85	...	...	...	...	...
5. *p*-Cymene	1.01	1.00	1.01	1.00	1.05	1.00
5a. Unidentified	1.30	...	2.13	...	1.86	...
5b. Unidentified	2.69	...	2.53	...	...	...
6. Linalool	3.91	3.88	2.92	2.90	2.20	2.20
6a. Camphor	...	...	3.31	3.37	2.67	3.00
7. Terpinen-4-ol	5.53	...	4.26	...	3.25	...
8. α-Terpineol	...	...	6.12	6.09	4.61	4.58
9. Geraniol	...	...	11.9	11.8	7.78	7.55
10. Unidentified	...	...	...	...	33.2	...
11. Unknown A	...	...	...	...	38.2	...

component, camphor, was detected in the West Indian oil. Linalool was present in Samples A (10.6%), B (8.1%), and D (5.9%), while it was not observed in Sample C of East Indian variety. The same observation was made as far as geraniol is concerned. We found 3.6% present in the West Indian sample, while two samples of the East Indian variety contain 0.3 and 11.9%, respectively.

The amount of α-terpineol varies depending on the sample of the oil (Table IV). Westway and Williams (10) did not report the percentage of α-terpineol in the oil they investigated.

In 1907 (9), safrole was reported present in about 0.6% in the oil of Ceylon nutmeg. Our analysis confirmed its presence in the East Indian oils only. The amount ranges from 4.2 to 6.0%. This same report mentions the presence of about a total of 0.2% of eugenol and isoeugenol in the oil from Ceylon. A peak corresponding to the retention time of isoeugenol was not observed in the chromatograms. We have observed eugenol in varying amounts in all three samples of the East Indian variety. Samples A, B, and C contain 1.3, 3.8, and 0.3%, respectively, of eugenol.

One of the constituents of the oil, which was not yet reported in literature, was isolated from the oil, using gas chromatography; an infrared spectrum was run. This constituent, which ranges from as low as 1.7% in the West Indian sample to as high as 25.9% in Sample C of the East Indian variety, was tentatively labeled as "Unknown A."

SUMMARY

Four commercially available samples of nutmeg oil were analyzed by gas-liquid chromatography, using 20% Reoplex 400 column. Relative retention times and enrichment procedure were used to identify the constituents of the oils. In some instances infrared spectra were employed.

The following components were present in the three samples of East Indian variety and in the West Indian sample: α-pinene, β-pinene, limonene, *p*-cymene, terpinen-4 ol, α-terpineol, and Unknown A. Terpinolene was found in small amounts and only in two samples of East Indian oil, while linalool and geraniol are absent in one sample of East Indian nutmeg oil. Safrole and eugenol were present in all three samples of the East Indian variety but were not observed in the West Indian sample. Camphor was found in the West Indian oil only.

Differences are also observed between the percentages of the components present not only compared to those listed in the literature but also between the oils analyzed.

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ERRATUM

In the paper titled "Absorption, Metabolism, and Excretion of the Semisynthetic Penicillin 6 (2-Ethoxy-1-naphthamido)penicillanic Acid (Nafcillin)" (1), a broken line represents intramuscular and a solid line represents oral groups of dogs in Figs. 1–3.

(1) Walkenstein, S. S., Wiser, R., LeBoutillier, E., Gudmundsen, C., and Kimmel, H., THIS JOURNAL, 52, 763 (1963).

perfume for various external medicines. The spirit has also been used in nervous headache, faintness and other nervous disorders, either held to the nostrils, or applied on soft linen to the head and forehead. It is also pleasing to the feeble and convalescent patient when sprinkled on the bed-covering or atomized in the sickroom.

Storage.—Preserve "in tight, light-resistant containers." *N.F.*

COMPOUND MYRCIA SPIRIT. N.F.

[Spiritus Myrciæ Compositus]

Mix 8 ml. of myrcia oil and 0.5 ml. each of orange oil and pimenta oil with 610 ml. of alcohol and gradually add water to 1000 ml. Set the mixture aside in a well-closed container for 8 days, then filter, using 10 Gm. of purified talc if necessary to produce a clear liquid. *N.F.*

Alcohol Content.—From 54 to 59 per cent, by volume, of C_2H_5OH. *N.F.*

For uses of this spirit see under *Myrcia Oil.*

Storage.—Preserve "in tight, light-resistant containers." *N.F.*

MYRISTICA. N.F. (B.P.)

Nutmeg. [Myristica]

"Myristica is the dried ripe seed of *Myristica fragrans* Houttuyn (Fam. *Myristicaceæ*), deprived of its seed-coat and arillode and with or within a thin coating of lime." *N.F.* The B.P. recognizes Nutmeg as the dried kernels of the seeds of *Myristica fragrans* Houtt.

B.P. **Nutmeg.** Semen Myristicæ; Nux Moschata. *Fr.* Muscade; Noix de muscade. *Ger.* Muskatnusz. *It.* Noce moscata. *Sp.* Nuez moscada; Nuez de especia; Nuez de Banda.

The nutmeg tree is about thirty feet high, with numerous branches, and an aspect somewhat resembling that of the orange tree. The leaves are alternate, petiolate, oblong-oval, pointed, entire, bright green and somewhat glossy on their upper surface, whitish beneath, and of an aromatic taste. The staminate and pistillate flowers are upon different trees. The former are disposed in axillary, peduncled, solitary clusters; the latter are single, solitary, and axillary; both are minute and of a pale yellowish color. The fruit, which appears on the tree mingled with the flowers, is round or oval, of the size of a small peach, smooth, yellow when ripe, and marked with a longitudinal furrow. The external covering, which is at first thick and fleshy and abounds in an austere, astringent juice, afterwards becomes dry and coriaceous, and, separating into two valves from the summit, discloses a scarlet reticulated arillode, commonly called *mace*, closely investing a thin, hard, brown, shining shell, which contains the seed or *nutmeg*.

The tree is produced from the seed. It does not flower until the eighth or ninth year, after which it bears flowers and fruit together, without intermission, and is said to continue bearing for seventy or eighty years. Little trouble is requisite in its cultivation. A branch of the staminate tree is grafted into all the young pistillate plants when about two years old, so as to insure their early fruitfulness. Hart reported in 1907 a group of nutmeg trees growing in Trinidad bearing both staminate and pistillate flowers and suggested that an attempt should be made to perpetuate this variety by grafting.

The nutmeg tree is a native of the Moluccas and other neighboring islands, and abounds especially in that small cluster distinguished by the name of Banda, whence the chief supplies of nutmegs were long derived. But numerous varieties of the plant are now cultivated in Sumatra, Java, Singapore, Penang, Ceylon, and other parts of the East Indies, and have been introduced into the Isles of France and Bourbon, Cayenne, and several of the West Indian islands. The *Myristica fragrans* was introduced into Grenada about 1843, and now this island is the principal place of cultivation of nutmeg in the Western Hemisphere. Various species of the genus *Myristica*, other than the official one, yield commercial seeds or products. The larger part of the nutmegs of commerce before the Second World War still came from the Dutch Banda Islands. The Penang nutmegs are distinguished by not being limed.

In the Moluccas the tree yields three crops annually. There the fruit is gathered by hand, or by means of a hooked stick before the husk splits and the outside covering rejected. In Grenada the husk is allowed to split while the fruit is on the tree and the ripe fruit is collected from the ground. The arillode, constituting the mace of commerce, is then carefully separated, so as to break it as little as possible. It is flatteend, dried in the sun, and afterwards sprinkled with salt water, with the view of contributing to its preservation. The "nuts" are dried in the sun, in ovens or in brick buildings. In the latter instance they are placed in trays over low charcoal fires with occasional turning. Drying is considered completed when the kernel rattles in the shell. They are then broken open, and the kernels, having been removed and steeped for a short time in a mixture of lime and water or dusted with dry lime, in order to preserve them from the attacks of worms, are graded and packed in casks or chests for exportation. They keep better if rubbed over with dry lime than when prepared in the moist way. Despite this protection, commercial nutmegs are sometimes wormy. Nutmegs from the East Indies are usually limed while those from the West Indies are not limed. During 1952 this country imported 5,413,327 pounds of unground nutmegs mostly from Indonesia, Leeward Islands, Trinidad, India, New Guinea, Malaya, Africa, and Netherlands.

Shriveled or damaged nutmegs and nutmegs in the shell (whole seeds deprived of arillodes) are imported for distilling purposes.

Description.—"*Unground Myristica* is ovoid or ellipsoidal in shape and is from 20 to 35 mm. in length and from 15 to 28 mm. in thickness. Externally it is light brown to dark brown. The surface is reticulately furrowed, the broad end with a large, circular, upraised scar from which arises a raphe extending to a depression at the opposite end. The cut surface has a waxy luster and a mottled appearance, given by the dark perisperm and the lighter colored endosperm. The odor is characteristically aromatic and the

taste pungently aromatic." *N.F.* For histology see *N.F. X.*

"*Powdered Myristica* is brown to moderate yellowish brown and consists of irregular fragments; perisperm with large, circular or elliptical volatile-oil reservoirs, small thin-walled parenchyma cells with reddish orange to orange or brown contents and occasional spiral tracheids and vessels. The endosperm shows more or less polygonal parenchyma cells containing starch, large aleurone grains, fat, and occasionally brown to yellowish orange pigment. Fixed oil globules are numerous, and the starch grains are single or 2- to 3-compound, or in aggregates, the individual grains, spherical, planoconvex or polygonal, from 3 to 22 μ in diameter, with a distinct, sometimes cleft hilum." *N.F.*

The microscopical structure of nutmeg and mace have been well illustrated by Winton and Moeller in the *Microscopy of Vegetable Foods.* It has been stated that much of the ground nutmeg of commerce has been made from small, stunted and worthless nutmegs, so-called "grinding nutmegs." The powdered drug has been adulterated with corn meal, powdered beans, curcuma and various nutshells.

Nutmegs have been punctured and boiled in order to extract their essential oil, and the orifice afterwards closed so carefully as not to be discoverable except by breaking the kernel. The fraud may be detected by their lightness. The largest nutmegs now command the highest prices. They should be rejected when very light in weight, with a feeble taste and odor, worm-eaten, musty, or marked with black veins.

Standards and Tests.—*Acid-insoluble ash.*—Not over 0.5 per cent. *Non-volatile, ether-soluble extractive.*—Not less than 25 per cent. *N.F.*

Constituents.—Nutmeg contains from 5 to 15 per cent of a volatile oil to which it owes its medicinal value (see *Myristica Oil*), from 25 to 40 per cent of a fixed oil and from 5 to 15 per cent of ash, the remainder being starch, fiber, water, etc.

The *concrete,* or *expressed, nutmeg oil* (*Oleum Myristicæ Expressum,* B.P. 1885, *Oleum Nucistæ*), often called *oil of mace,* or *nutmeg butter,* is obtained by bruising nutmegs, exposing them in a bag to steam, and then compressing them strongly between heated plates. A liquid oil flows out, which becomes solid when it cools. This oil may also be obtained by solvent extraction of the nutmeg. The best nutmeg butter was imported from the East Indies; it is a soft solid, unctuous to the touch, of a yellowish or orange-yellow color, more or less mottled, with the odor and taste of nutmeg. It melts at about 45° and has a specific gravity of 0.995. In 1874 Playfair separated from this a crystallizable fat, *myristin,* which is the glyceride of *myristic acid,* $C_{14}H_{28}O_2$. Power and Salway (*Trans. Chem. Soc.*, 1908, p. 1653) found the expressed oil of nutmeg to contain 73 per cent of trimyristin, 12.5 per cent of essential oil, smaller quantities of oleic acid, linoleic acid, resinous material with traces of formic, acetic and cerotic acids, with 8.5 per cent of unsaponifiable residue. Myristin is also found in spermaceti, in coconuts, in poppy oil and in the fixed oil of linseed. It may be obtained directly from nutmeg by extracting with benzene, filtering the liquid, and allowing it to crystallize by spontaneous evaporation.

For a description of certain allied botanical products, variously designated as nutmeg of one variety or another, or related to nutmeg, see *U.S.D.*, 24th ed., p. 726.

Uses.—Nutmeg owes its medicinal and toxic properties solely to the volatile oil which it contains. For a discussion of the effects and uses of this, see *Myristica Oil.* Powdered nutmeg is rarely used in medicine alone, although it has been used in dysentery (see Leidy, *Med. Rec.*, March 1, 1919). It is an ingredient of several official preparations. The expressed oil is occasionally used as a gentle external stimulant and was an ingredient in the *Emplastrum Picis* of the 1885 British Pharmacopœia.

Nutmeg has been given in *doses* of 0.3 to 1.3 Gm. (approximately 5 to 20 grains).

Off. Prep.—Myristica Oil, *U.S.P., B.P.;* Compound Lavender Tincture; Aromatic Rhubarb Tincture, *N.F.;* Aromatic Powder of Chalk, *B.P.*

MYRISTICA OIL. U.S.P. (B.P.)

Nutmeg Oil, [Oleum Myristicæ]

"Myristica Oil is the volatile oil distilled with steam from the dried kernels of the ripe seed of *Myristica fragrans* Houttuyn (Fam. *Myristicaceæ*)." *U.S.P.* The B.P. recognizes the same product.

B.P. Oil of Nutmeg. Oleum Macidis (*Ger.*); Oleum Myristicæ Æthereum. *Fr.* Essence de muscade. *Ger.* Atherisches Muskatöl; Macisöl; Muskatblütenöl. *It.* Essenza di noce moscata. *Sp. Esencia de Nues Moscada.*

For a description of the nutmeg plant see *Myristica.*

The oil is obtained from powdered nutmegs by distillation with water, usually after the removal of their fat. Nutmeg oil is sometimes made from the light, worm-eaten nuts, of which large quantities are rejected in sorting the different qualities in Holland; the worm robs the nutmeg of its fat oil, while the essential oil remains in the nut in full. Nutmeg yields from 3 to 8 per cent of volatile oil.

Description.—"Myristica Oil is a colorless or pale yellow liquid having the characteristic odor and taste of nutmeg. One volume of Myristica Oil dissolves in 1 volume of alcohol. One volume of East Indian Myristica Oil dissolves in 3 volumes of 90 per cent alcohol. One volume of West Indian Myristica Oil dissolves in 4 volumes of 90 per cent alcohol." *U.S.P.*

Standards and Tests.—*Specific gravity.*—Not less than 0.880 and not more than 0.910 for East Indian oil, and not less than 0.854 and not more than 0.880 for West Indian oil. *Optical rotation.*—Not less than +8° and not more than +30° for East Indian oil, and not less than +25° and not more than +45° for West Indian oil, at 25°, and using a 100-mm. tube. *Refractive index.*—Not less than 1.4740 and not more than 1.4880 for East Indian oil and not less than 1.4690 and not more than 1.4760 for West Indian oil, at 20°. *Residue on evaporation.*—Not over 60

mg. from 3 ml. of East Indian oil, and not over 50 mg. from West Indian oil. *U.S.P.*

Constituents.—Power and Solway (*Trans. Chem. Soc.*, 1907, 2037) analyzed volatile oil of nutmeg and found that about 80 per cent of it is dextro-camphene and dextro-pinene, with about 8 per cent of dipentene, besides small proportions of eugenol and iso-eugenol, linalool, borneol, terpineol, geraniol and safrol; they found about 4 per cent of *myristicin*, small amounts of free myristic acid, and traces of esters of this and other fatty acids.

Myristicin, $C_{11}H_{12}O_3$, is of interest as the poisonous ingredient of nutmeg (see under *Uses*). It is the methylene ether of 3-methoxy-4,5-dihydroxy-allylbenzene. It occurs with the related substance apiol in parsley.

Uses.—Besides its aromatic property, nutmeg oil possesses considerable narcotic power. It causes in the lower animals dilatation of the pupils, unsteadiness of the gait followed by sleepiness, with slow respiration, and, if the dose is large enough, loss of reflexes. According to Dale (*Proc. Roy. Soc. Med.*, Feb., 1909), doses large enough to produce narcosis in the cat are invariably fatal through fatty degeneration of the liver. A number of fatal cases of nutmeg poisoning have been reported in human beings (see Power and Solway, *Am. J. Pharm.*, 1908, p. 563). These authors cited a case in which 2 drachms of powdered nutmeg produced drowsiness deepening into stupor, the patient continuing for several hours alternately delirious and sleeping. Dale found that a dose of 1.9 Gm. per kilo caused in a cat a semi-comatose condition with death in 24 hours with fatty degeneration of the liver.

The toxic ingredient in oil of nutmeg is believed to be myristicin. Dale found that myristicin caused similar symptoms but the quantity required was much larger than would be contained in a toxic dose of powdered nutmeg, the fatal dose of myristicin for a cat being between 0.5 and 1 ml. per kilo; Power and Solway suggested that this difference may have been due to imperfect absorption and stated that 2 minims (0.12 ml.), hypodermically, produced in the cat extensive degeneration of the liver (see also Christomanos, *Arch. exp. Path. Pharm.*, 1927, 123, 252).

Nutmeg oil is used as a flavoring agent; also as a carminative and as a local stimulant to the gastrointestinal tract.

Dose, 0.03 to 0.2 ml. (approximately ½ to 3 minims).

Labeling.—"Label Myristica Oil to indicate whether it is East Indian or West Indian Oil." *U.S.P.*

Storage.—Preserve "in tight containers." *U.S.P.*

Off. Prep.—Aromatic Ammonia Spirit, *U.S.P.*, *B.P.*; Pepsin and Rennin Elixir, *N.F.*

MYRRH. N.F.

Gum Myrrh. [Myrrha]

"Myrrh is the oleo-gum-resin obtained from *Commiphora molmol* Engler, *Commiphora abyssinica* (Berg) Engler or from other species of *Commiphora* (Fam. *Burseraceæ*)." *N.F.*

Gummiresina Myrrha. *Fr.* Myrrhe. *Ger.* Myrrhe; Myrrhengummi. *It.* Mirra. *Sp.* Mirra.

The name myrrh is possibly derived from the Arabic and Hebrew word "*Mur*" meaning bitter. The drug is called "*Mulmul*" and "*Ogo*" by the natives of Somaliland and "*Heerabol*" by the Indian traders.

Though myrrh has been employed from the earliest times, not all the plants yielding it have been definitely determined. According to Engler (*Die Natürlichen Pflanzenfamilien*, 1931, 19, 437), *Commiphora molmol* Engl. yields the genuine Somali myrrh or "molmol." This species occurs in northern Somaliland. According to Deflers and Schweinfurth (*Ber. deutsch. pharm. Ges.*, 1893), *C. abyssinica* (Berg) Engl., occurring in southern Arabia, Eritrea and northern Abyssinia, yields genuine Arabian myrrh. Formerly, *Myrrha* (Nees) Engl. of southern Arabia and Yemen was thought to be the principal myrrh-yielding species, but Engler stated it is not aromatic and yields no myrrh. It seems probable that other species of *Commiphora* found in northern Africa, Arabia and Yemen also yield myrrh. One of these, *C. Schimperi* (Berg) Engl., which occurs in Abyssinia and Yemen, appears to be an additional likely source of the drug.

The genus *Commiphora* Jacq. contains about 80 species and is distributed in tropical Africa and to a lesser extent in tropical Asia.

Commiphora molmol Engler, the *didin* of Somalis, which appears to be the main source of myrrh, is a sparingly branched, xerophytic, low tree, up to about 3 meters in height with grayish green, chiefly trifoliate leaves with large, lanceolate to cuneate-lanceolate leaflets, the terminal leaflets being frequently toothed toward the summit, the lateral leaflets being mostly very small. The flowers are small and axillary. The fruit is a 2-valved drupe possessing one sterile compartment and a thick endocarp. The sterile compartment is weakly arched and smooth on its outer surface, the fertile compartment contains a single, enclosed seed and is strongly arched and warty on its outer surface.

Commiphora abyssinica (Berg) Engl., the source of some Arabian myrrh and probably of some African myrrh, is a related species, up to 10 meters in height, which is characterized by its pale, spinose branches, alternate, simple to trifoliate leaves, the latter with sessile leaflets, each of which is ovate-oblong to lanceolate with a cuneate base and crenate-serrate margin. Its flowering branches are short and often 3-flowered; the flowers small with a finely scabrous calyx. Its fruits are ovoid drupes with short, acutely tipped summits.

Commiphora Schimperi (Berg) Engl., known in Abyssinia as "*oanka*" and in Yemen as "*gataf*," is characterized by its short, glabrous and spiny branches, membranous, trifoliate leaves with oblong to rhomboid leaflets, its glomerules of small flowers and its sub-ovoid, apiculate, drupe fruits.

Myrrh is collected in Somaliland and Arabia by making incisions into the bark of the stems of the trees. Within this bark occur schizogenous secretion reservoirs in which a yellowish-white oleo-gum-resin is formed. These are punc-